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TITLE: **Epidemiological Study of Mild Traumatic Brain Injury Sequelae Caused by Blast Exposure During Operations Iraqi Freedom and Enduring Freedom**

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14. ABSTRACT: Accomplishments include initial and continued IRB approvals, completion of enrollment, study assessments, data collection, data management and all preliminary analyses. Two hundred and thirty eight (238) participants passed eligibility pre-screen and consented for study procedures. Of these, twenty-two (22) participants either did not meet final eligibility or failed to complete Phase 1 (baseline) evaluations resulting in the final enrollment sample size of two hundred and sixteen (216) participants. The overwhelming majority (77%) of the final sample met criteria for post-concussion syndrome (PCS). From the analyses, we have so far achieved 6 full-length publications in peer-reviewed scientific journals, another submitted manuscript is under review, and multiple pending manuscripts are in varying stages of completion. **Summary of Findings:** The more significant findings include: 1) screening questionnaires for PTSD and mTBI after military blast-exposure have important diagnostic limitations, 2) a novel fully structured interview algorithm was developed and validated for determining the retrospective diagnosis of blast mTBI, 3) Post-concussive like symptoms, PTSD, depression and pain are common after blast exposure during deployment, do not diminish over time, and none are clearly related to having sustained blast mTBI, 4) Persisting neuropsychological and balance impairments and physiologic changes on quantitative EEG are common after military blast exposure and each have profiles related to and hence potentially attributable to blast mTBI especially when accompanied by post-traumatic amnesia (PTA). **Conclusions:** PCS like symptoms are ubiquitous after military blast exposure, do not dissipate over one year follow-up, and have poor specificity for blast mTBI. Cognitive and balance deficits are common after military blast exposure and are influenced in part by blast mTBI. This implies a need to measure balance and neuropsychological performance after blast exposure to assess for potential impairments and avenues of treatment, particularly when there is history of blast mTBI with PTA. Altered QEEG patterns related to blast mTBI implicate physiologic underpinnings of these potential persisting mTBI effects.

15. SUBJECT TERMS
Mild traumatic brain injury, blast exposure, head injury, post-traumatic stress disorder, post-concussion syndrome, military personnel, functional outcomes

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TABLE OF CONTENTS:

I. INTRODUCTION:

Blast related Traumatic Brain Injury (TBI) is an important source of morbidity in Operations Iraq Freedom and Enduring Freedom (OIF/OEF). Mild TBI (MTBI) may go unrecognized and persist as post-concussion syndrome (PCS). Given that available information is largely anecdotal, the identification, characterization, and prediction of individuals who have PCS with persisting effects from blast-related MTBI are the focus of this series of epidemiological investigations. Multiple hypotheses are being tested including:

- a significant proportion (>18%) of service members experiencing blast events during OIF/OEF sustain a MTBI that leads to persisting symptoms consistent with PCS;
- multiple predictive factors for developing PCS can be identified;
- returnees with PCS will display objective impairments on neuropsychological testing, computerized posturography and/or quantitative electroencephalography; and,
- those with PCS will demonstrate improvement over time but will continue to display significant long-term disability.

A cross-sectional sample of 747 OIF/OEF returnees, who experienced a blast event on tour within the past two years, will undergo three phases of evaluations as follows:

- Phase-I: will determine the sample prevalence of PCS after blast related MTBI, characterize the constellation of related symptoms and problems, and allow predictive modeling.
- Phase-II: will utilize a case-control design to evaluate objective abnormalities among the subjects with PCS after MTBI.
- Phase-III is a longitudinal design using repeated measures for analysis of outcomes over time (baseline, 6 months, and one year).

II. BODY OF REPORT: .Accomplishments relative to our Statement-of-Work (SOW):

A. *SOW Task 1* - Objective: prepare and initiate the overarching research study plan.

1. Obtain IRB approval for project [Research Assistants, Mr. Heimiller, Dr. Walker]:

Accomplished. All amendments, updated staff rosters, SAEs, and continuing reviews have been submitted to primary and secondary IRBs as required and approved.

2. Establish Military site screening/recruitment options [Dr. Walker & Research Assistants]:

Accomplished.

The CDMRP research team began the recruitment and screening process at Kenner Army Health Clinic at Fort Lee on 6/19/2009. 9 subjects were recruited from Fort Lee.

We began recruiting at US Marine Corps Base (MCB), Quantico, Virginia on June 9, 2010). 11 subjects were recruited from this site.

Recruitment at MCB Camp Lejeune, NC commenced in April 2011. 91 subjects were recruited from MCB CL.

3. Establish availability and content of acute injury (war-zone) variables. [Dr. Walker]

Accomplished.

4. Finalize Data collection forms including TELEforms. [Drs. McKinney, Cifu, Manning Franke & Walker]

Accomplished.

5. Complete set-up of data management software system. [Mr. Bush]

Accomplished.

6. Establish logistics (when, where, workspace) for study screening and recruitment of military personnel at Central Virginia PDHA clinic sites. [Dr. Cifu, Dr. Walker, Dr. Manning Franke & Research Assistants]

Accomplished. Volume of eligible subjects identified at Kenner Army Health PDHRA clinics was far below anticipated.

7. Hire and train study coordinator and other TBH study personnel. [Hiring: Mr. Heimiller, Dr. Walker. Training: Drs. Nelson, Walker & McDonald]:

Accomplished.

CDMRP/Walker: Study Staff (Compensated) Summary

NAME & ROLE	MONTH/YEAR HIRED
William C. Walker, MD, Principal Investigator	September, 2008
David X. Cifu, MD Co-Investigator	September, 2008
Jessica McKinney-Ketchum, PhD, Biostatistics	September, 2008 (*Departed program Subaward Year-6*)
Brian J. Bush, MSMIT Data Manager	June, 2009
Adam Sima, PhD Biostatistics	Subaward Year-6 (*replaced Dr Ketchum*)
Huan Wang Data Analyst	Subaward: Year-3
Michelle Nichols, MSN, RN, Co-Investigator & Clinical Research Coordinator	September, 2008. *(Departed program in March, 2012)*
Jerome Heimiller, RPH, MPA, Administrator	September, 2008. *(Departed program in Oct., 2012)*
Tiffany Clory, BS, Research Assistant	November, 2008 *(Departed Program: July, 2010)*

April Dean, BS, Research Assistant	January, 2009. *(Departed Program: Feb, 2013)*
Tammy Searles, RN, Lead Research Assistant	June, 2009 *(Departed Program: Jan., 2009)*
Scott McDonald, PhD., Research Psychologist	September, 2008
Emily Lynn, BA Research Assistant	April, 2010. (*Departed program: July, 2012)*
Jasmine Smith, BA Research Assistant	June, 2010 *(Departed Program: Sept, 2011)*
Judy Pulliam Research Assistant	June, 2012
Laura Manning Franke, PhD Co-Investigator	March, 2012

***B. SOW Task 2* - Objective: Determine the prevalence of PCS after blast related MTBI in OIF/OEF to better define the scope of residual injury and determine early factors predictive of PCS after blast injury to aid the development of better secondary prevention and treatment strategies. Timeline for all subtasks: Gradually accrue over 4 years 747 subjects total (50 subjects by end Year 1, 325 subjects by end Year 2, 600 subjects by end Year 3, 747 subjects by end Year 4) into Phase-I. Responsible personnel: listed below for each subtask [ ].**

1. Consent & Enroll 747 Subjects Total. [Dr. Walker, Dr. Manning Franke, Research Assistants]

As previously reported we have closed the study for further enrollments. A total of **238** subjects who met preliminary eligibility criteria **consented** for enrollment. After 22 subjects were either determined to be ineligible or dropped out prior to completing Phase 1, the **final sample size was n=216.** We have previously reported on the reasons enrollment was below target.

2. For each subject above, complete standardized current state questionnaires for qualitative and quantitative measurement of: Post-concussion syndrome (PCS) using the Rivermead Post-Concussion Symptoms Checklist (RPQ) (King, 1995), Combat Stress using the PTSD Checklist Military Version (PCL-M) (Weathers et al, 1991), pain using both the McGill Pain Questionnaire short form (MPQ-SF) (Melzak, 1987) and the 11 point Numerical Scale (Jensen MP et al, 1989), and affective disorder using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The ICD-10 criteria for PCS will be used to categorize the cases with PCS for the prevalence numerator, subjects with PCS after OIF/OEF blast exposure Injury (Boake, 2005; WHO, 1992; WHO, 1993). The International Classification of Diseases is published by the World Health Organization (WHO). The ICD-10 criteria for PCS are 1) a history of MTBI and 2) a minimum of 3 of following symptoms (present to a moderate degree compared to pre-morbid): headache, dizziness, fatigue, irritability, insomnia, poor concentration, memory problems, or intolerance of stress, emotion, or alcohol. The RPQ is being utilized to standardize this diagnostic assessment. [Oversight: Research Coordinator, Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on **216** subjects.

3. For each subject, collect blast injury and individual characteristics data including: dazed, memory gap (injury, pre-injury, and post-injury), lost consciousness, stress, pain, helmet wearing, shrapnel injury, tympanic membrane rupture, hearing loss, type of blast, immediate blast effects, number of blast exposures, demographic, education level, psychiatric history, medical history, and time since injury. These variables will be collected using a series of questionnaires including: Full Blast Questionnaire (modified version of Walter Reed Blast Inventory (Scherer et al, 2007), see Protocol), a Health History Questionnaire (see Protocol), the recalled immediate psychological stress of the blast event using the Impact of Events Scale (IES) (Horowitz et al, 1979), the recalled physical pain level of the blast event using the 11 point Numerical Scale and the Alcohol Use Disorders Test-Consumption (AUDIT-C), a brief screening tool for heavy drinking and/or active alcohol abuse/dependency (Bradley et.al., 2007). [Oversight: Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on **216** subjects.

4. For each subject, the study biostatistician will designate a group assignment (with PCS versus without PCS) using a predetermined threshold of MTBI symptom severity (ICD-10 diagnostic criteria applied to the RPQ data) in order to derive prevalence of PCS and to select subjects for Task 3 [Dr. McKinney]

Accomplished on **216** subjects.

5. Study biostatistician will provide interval (monthly) updates of the ratio of PCS to no PCS group membership to the PI for the purpose of monitoring accrual targets and trends, but will otherwise will not reveal assignment to either subject or study staff (double blind). [Dr Sima]

Accomplished on **216** subjects.

6. Perform data audits after first subject completed Phase 1 and on 5% of accrual target (37 subjects) on a monthly basis. [Dr. McKinney-Ketchum]

Accomplished on **216** subjects.

7. Using a case-control design (PCS versus no PCS) and adjusting for PTSD, several statistical analyses will be performed including two-way analysis of variance (ANOVA) (to compare quantitative variables), chi-square tests (to compare proportions of qualitative variables, and a multiple logistic regression model (to determine the predictive nature of these variables as a group). PTSD will be measured as a continuous variable using the PTSD Checklist – Military Version (PCL-M) total score. These analyses will determine factors associated with (or predictive of) developing PCS after blast related MTBI. [Statistics: Dr. Sima. Interpretation: all key investigators]

We operationally defined PCS as at least 3 symptoms endorsed on the RPQ at a “moderate” or “severe” problem level (item score of 3 or 4) that was not isolated to the emotional domain (at least 1 positive symptom is in somatic or cognitive domain). Within the entire cohort regardless of whether or not a blast mTBI was identified, 166 participants (77%) had symptoms consistent with PCS. Among the 176 participants (81%) diagnosed with having sustained a blast mTBI, 140 participants (80%) had symptoms consistent with PCS. Comparatively, the proportion of participants who did not sustain blast mTBI and had symptoms consistent with PCS was smaller (26 out of 40 or 65%; P=0.049).

The constellation of PCS-like symptoms after military blast exposure appears to be more complex than experienced by civilians. Already published data analyses from this study already show that the PCS symptom complex as measured by the Rivermead Postconcussion Questionnaire (RPQ) consists of four factors rather than the traditional three factors (somatic, cognitive, emotional).(Franke, Czarnota, Ketchum, & Walker, 2014) In our blast-exposed cohort, the somatic factor split between visual and vestibular factors suggesting a unique condition or PCS subtype(s).

In terms of predicting PCS, the role of blast mTBI remains in doubt. Analyses we completed before completion of enrollment and implementation of our structured interview indicated that alteration of consciousness (AOC) questionnaire items were associated with PCS symptom severity; suggesting a link with mTBI. This information can be found in a published manuscript in the appendix of this report (W. Walker, McDonald, Ketchum, Nichols, & Cifu, 2012). Subsequent analyses using a refined structured interview based TBI diagnosis on a subset of participants contradicted this finding. In two separate analyses that are part of pending publications found in the Appendix, we found no difference in PCS symptom severity across mTBI groups (Franke et al., 2014; W. C. Walker, Cifu, & et, IN PRESS). However, more complete analysis of the full sample with their finalized blast mTBI diagnosis again suggests a link between blast mTBI diagnosis and PCS symptom severity (see above chi-square test; see Supporting Data section of report VIII B Tables 2 and 3 and as well as VIII F Table 6 “Average” column). There are several possible explanations for these discrepancies including type 2 error in the limited interview dataset. Alternatively, the algorithm used to extrapolate mTBI diagnosis from questionnaire items for the half of the sample that was not interviewed may be biased toward symptomatic participants. Further study is recommended with a larger sample all of whom are interviewed to establish their mTBI diagnoses.

Our analyses show mixed findings on the relationship between PCS symptoms and other variables. Another published manuscript from this study found in the Appendix shows that select PCS symptoms (vestibular and visual) are related to balance decrements on computerized posturography (Franke et al., 2014). In one of our IN PRESS publications from this study we showed that PCS symptoms are higher in persons with a PTSD diagnosis established on interview (W. C. Walker, McDonald, & Franke, IN PRESS). PCS symptom severity was also related to depression and PTSD symptom severity (see also supporting data section VIII F Table 6, “Averaged” column). However subsequent analyses did not show an association between PCS and mood or anxiety diagnoses based on DSM-IV structured interview; these results will be submitted for publication as part of a manuscript under preparation. Thus, this link between PCS and other mental health disorders is more likely an artifact of symptom overlap between conditions. Lastly, recent analyses showed that PCS symptom severity is not related to impairment on neuropsychological testing. These results will also be submitted for publication as part of another manuscript under preparation

In summary, PCS symptoms after military blast exposure are highly prevalent and differ in factor structure from civilian samples with somatic symptoms splitting into visual and vestibular factors. There appears to be at least in part an organic basis to some PCS symptoms with an association found between worse vestibular symptoms and lower postural stability. On the other hand, PCS cognitive symptoms did not predict cognitive performance. Although we found contradictory results on the relationship between mTBI and PCS symptom severity, PTSD is clearly associated with worse PCS symptom severity. Other mood and anxiety disorders do not appear to be strongly linked to PCS.

C. Task 3 **- Objective: Identify and describe objective cognitive performance and neuro-physical impairments in returnees with PCS after blast-related MTBI incurred during OIF/OEF (Study Phase 2). Timeline: Gradual accrual into Phase 2 of minimum of 284 total**

subjects over 4 years (30 subjects by end Year 1, 125 subjects by end Year 2, 225 subjects by end Year 3, 284 subjects by end Year 4). Responsible personnel: listed below for each subtask [ ].

1. At least monthly, groups of subjects who completed Phase-I (Task 2 above), will be assigned to enter Phase-II evaluations as follows: With PCS (all), Without PCS (equal number to "With PCS" who are selected using described randomization scheme). [Research Assistants & Dr. Walker]

   Accomplished on **216** subjects.

2. Study biostatistician will provide the study coordinator with a list (at least monthly) of de-identified subjects who are assigned for Phase-I evaluations, but will NOT reveal group assignment (With PCS versus Without PCS) to study staff or subject (i.e. to minimize bias of objective evaluations during Phase 2, double blinding of group assignment will be maintained). [Dr. Ketchum and Sima]

   Accomplished on **216** subjects.

3. For each Phase-II subject, conduct objective evaluations and collect data including full neuropsychological batteries (cognitive performance and fine motor assessment), quantitative electroencephalography (neurophysiologic cognitive assessment), and computerized posturography (balance impairment assessment). CPT will consist of The Sensory Organization Test (SOT), a composite index that defines abnormalities across somatosensory, visual, and vestibular systems. QEEG recordings will consist of baseline 10 minute eyes closed and a 10 minute eyes open resting period. There are multiple normative databases for comparison of individual electrocortical activity. The "life-span" database included with the Neuroguide® EEG analysis software consists of 625 records from normal individuals ranging in age from 2 months to 89 years. Neuroguide® also includes a discriminant function analysis to calculate the probability that a person has sustained a TBI based on their eyes closed resting baseline recording alone. In the initial validation study, a sensitivity of 95.45% and a specificity of 97.44% were reported for classification accuracy in comparison to normals. This discriminant function was developed based on the work of Thatcher and others with the Defense and Veterans Head Injury Program (DVHIP) in the 1990's and used a sample of veterans from what have become the lead Polytrauma centers within the Veterans Affairs health care system (Palo Alto, CA, Minneapolis, MN, Richmond, VA, and Tampa, FL). Thus, it is an appropriate comparison group for our purposes. The neuropsychological battery will consist of the following standardized, validated, tests of proven reliability: Wechsler Test of Adult Reading (WTAR, pre-morbid IQ estimate),(Mathias, Bowden, Bigler, & Rosenfeld, 2007) Conners Continuous Performance Test-II (CCPT-II, sustained attention),(Conners, 2000) Paced Auditory Serial Addition Test (PASAT, processing speed),(Vanderploeg, Curtiss, & Belanger, 2005) Halsted-Reitan Trail Making Test A & B (TMT, visual scanning and executive function),(Lange, Iverson, Zakrzewski, Ethel-King, & Franzen, 2005) Stroop classic test (target processing speed and divided attention),(Soeda et al., 2005) Grooved Pegboard to asses fine motor speed and dexterity (Hanna-Pladdy, Mendoza, Apostolos, & Heilman, 2002), Test of Memory Malingering (TOMM) (Tombaugh, 1997) California Verbal Learning Test-II (CVLT-II) (learning and working memory),(Vanderploeg et al., 2005) Wechsler Adult Intelligence Scale III (WAIS-III) items: Digit Symbol Coding, Digit Span, Letter-Number Sequencing, Symbol Search, & Arithmetic (processing speed, attention, and working memory),(McKay, Casey, Wertheimer, & Fichtenberg, 2007) Delis-Kaplan Executive Function System (D-KEFS) Category Fluency (Animals And Boys' Names) (Harrison, Buxton, Husain, & Wise, 2000):Controlled Oral Word Association Test single letter and category items (COWAT, verbal fluency),(Iverson, Franzen, & Lovell, 1999) Benton Visual Memory Test-Revised (BVMT-R) (visual perception

and memory).(Morey, Cilo, Berry, & Cusick, 2003) [Test scheduling: Research Assistants; Neuropsychological testing: Trained Research Assistants, , & Drs. McDonald and Manning Franke. QEEG testing: research assistants.]

Accomplished on the **177** subjects who have completed Phase-II. [Note: 8 subjects had a contraindication for computer posturography and 2 subjects were unable to tolerate the entire computer posturography test. 3 subjects refused or did not comply with neuropsychological testing.]

4. Use this data to perform and fit several two-way ANOVA models with main effects for PCS (present/absent) and cognitive or neurological impairment (present/absent). A separate model will be fit for each response variable. [Statistics: Dr. Sima. Interpretation: all key investigators]

4a. *Cognitive impairment analyses.*

These results will be submitted for publication as part of a manuscript under preparation. A synopsis of the findings follows:

For the 174 subjects noted in Task 3.4 who completed neuropsychological testing, 18 subjects failed the effort validity measure and were removed from most analyses involing neuropscyhological test results. Given the multitude of tests and subtests, primary measures were identified apriori for each neurocognitive domain of interest (e.g. sustained visual attention, delayed verbal memory, working memory, etc). The profiles on these primary measures for the final sample of 156 subjects with valid test results showed multiple abnormalities. Among the primary measures, the PASAT (Mean= -1.29, SD= 1.35), CVLT-II (Mean= -0.56, SD= 1.16), BVMT-R (Mean= -0.24, SD= 1.19), CPT-II (Mean= -0.26, SD= 0.81), Trail-Making Tests B (Mean= -1.34, SD= 1.91) and Grooved Pegboard Test (Mean= -0.51, SD= 1.37) each had lower values than the normative population ($P<0.05$) (see Figure 1 in Supporting Data section VIII C of this report for graphical represenation of this data). Conversely, participants in this sample had higher WTAR than the normitive population (Mean= 0.14, SD= 0.82; $P<0.05$) indicating that the deficts were not due to lower premorbid intellect. Furthermore, the PASAT (40%), Trails B (33%), CVLT-II, and BVMT-R (15%, each), Stroop Color-Word Interference trial (9%) and Grooved Pegboard (13%) had higher than expected incidence of participants considered impaired based on the lowest 5th percentile of the normative population. Thirty participants (19% of the sample) demonstrated overall cognitive impairment, defined as impairment on three or more of the individual primary measures. For reference, the expected normative base rate for three or more impaired scores on the primary measures from this test battery is 4.03%.

Regarding the hypothesized association between PCS and cognitive impairment, we found that participants classified as overall impaired did not differ on their total RPQ score ($p<0.05$). This finding is consistent with our already published manuscript showing that the RPQ cognitive factor score is not related to cognitive performance (Franke et al., 2014). Importantly, we did however find differences in the likelihood of overall cognitive impairment between the different blast mTBI grade groups (*p*-value =0.033). The relative risk of having scores that imply cognitive impairment is 2.59 (95% CI: 0.98, 6.85; P= 0.054) when comparing the mTBI with PTA group to the mTBI without PTA group; and 3.01 (95% CI: 0.90, 10.1; *p*-value = 0.074) when comparing the mTBI with PTA group to to the group who did not sustain blast mTBI. There was no significant difference in relative risk for the mTBI without PTA group compared to the group who did not sustain blast mTBI (RR= 1.16 ; 95% CI: 0.28, 4.85; *p*-value= 0.840). Additionally, analysis of individual primary neuropsycholgical scores showed significant differences between the blast-related mTBI groups for the CVLT-II (*p*-value= 0.048). Post-hoc testing showed that participants who had mTBI with PTA

(Mean= -0.75, SD-1.19) had significantly lower CVLT-II scores than those who did not sustain mTBI (Mean= -0.16, SD-1.16) (*p*-value= 0.015). No differences were observed between the mTBI without PTA group (Mean= -0.51, SD= 1.07) and either the mTBI with PTA group (*p*-value= 0.1813) or no mTBI group (*p*-value= 0.264).

In summary, although PCS symptoms were not predictive of cognitive performance, having sustained blast mTBI with PTA is associated with increased odds of having overall cognitive impairment and with lower auditory memory performance. This suggests that higher grade mTBI (with PTA) significantly increases the risk of residual cognitive impairment after military blast exposure. The lack of association with cognitive symptoms implies that all individuals s/p blast mTBI with PTA should undergo comprehensive neuropscyhological testing to assess for potential deficits and treatment needs.

4b. *Postural Stability*.

As detailed in our recently published manuscript found in the Appendix,(Franke et al., 2014) more severe vestibular and visual symptoms (RPQ factors scores) were associated with lower performance on computerized dynamic posturography (CDP). Thus, unlike cognitive symptoms where we found no link to cognitive performance, there appears to be an organic basis for at least some of the symptom domains of PCS.

We also recently completed analysis of the influence of blast mTBI and PTSD diagnoses on postural stability and a manuscript has just been submitted for publication (see Appendix for full manuscript; two figures (figure 2 & 3) from the manuscript are also shown in the Supplemenal Data section VIII D). A synopsis of this data follows in the next paragraph.

Data were analyzed from a subject pool of 166 participants who completed CDP testing and had valid balance performance effort measures. Using nonparametric tests and measures of impairment, we found that balance was deficient in participants diagnosed with blast mTBI with posttraumatic amnesia (PTA) or PTSD versus those with neither, and that deficits were amplified for participants with both diagnoses. In addition, unique CDP deficiencies were found for individuals having isolated blast mTBI with PTA and isolated PTSD.

Thus, computerized balance assessment appears to offer an objective technique to examine the physiologic effects and provide differentiation between participants with blast-related mTBI and PTSD.

5. <u>Determine the sensitivity and specificity for detecting neurophysiologic abnormalities after MTBI from blast injury during OIF/OEF using QEEG with the goal of assessing the accuracy of detection of mild TBI using a purely neuro-physical method of measurement</u>. [Statistics: Dr. Sima. Interpretation: all key investigators]

Resting state EEGs were collected from 176 participants. After reviewing for recording quality and validity (e.g. no deep sleep), 147 recordings were retained for analysis. Power profile was chosen as the outcome variable because it has been shown to differentiate states of awareness after severe brain injury (e.g. minimally conscious state vs. locked in state). Absolute power was computed from the EEG in each of 5 frequency bands: delta, theta, alpha, beta, and gamma. Band power across these bands was log transformed and analyzed as a multivariate power profile at each of 13 electrode sites.

Results: There was an effect of age on power profile: generally, the youngest and oldest participants had higher power in lower frequencies (U shaped function of age). Next, effects of PTSD and mTBI (none, TBI without post-traumatic amnesia (PTA), TBI with PTA) were computed on power profile while covarying age. Multivariate effects of both mTBI and PTSD

were generally significant across recording sites, i.e. both conditions are associated with the resting state EEG power. Univariate effects showed that **regardless of PTSD status, mTBI increases power in lower frequencies (delta, theta)**. This effect was linear for TBI severity; i.e. low frequency power was highest for mTBI with PTA, next highest for mTBI without PTA and lowest for no mTBI. Conversely, **regardless of mTBI status, PTSD reduced power in the lower frequencies**. The pattern for the comorbid mTBI and PTSD group also supported opposing neurophysiological effects for mTBI and PTSD. The comorbid group fell in between the single morbidity groups, with higher delta and theta power than those having neither condition or having PTSD alone, but less than those having mTBI with PTA alone. These results are shown graphically in the Supporting Data section of this report (VIII E; Figures 4, 5, & 6).

In general, these results suggest that chronic blast mTBI and PTSD have qualitatively different effects on the brain's resting state. Further, these effects appear to be opposed to each other, with mTBI increasing slow activity and PTSD decreasing it. Small sample sizes in some cells (especially PTSD only) limit the ability to interpret interactions.

6. Determine the feasibility of a functional magnetic resonance and diffusion tensor imaging pilot descriptive study (anatomic/physiologic assessment) in a subset of cases and controls. [Dr. Walker]

   Due to local shortage of radiology personnel, we canceled plans for this imaging pilot.

D. Task 4 - Objective: **Assess the sensitivity and specificity within this sample of select key diagnostic questionnaires used in Phase 1 relative to "gold standard" structured interviews.**

1. Structured interviews will be added to Phase-II measures for: Major Mental Health disorders (Major Depressive Disorder, Bipolar Disorder, Panic Disorder w/ w/o Agoraphobia Social Anxiety Disorder, Specific Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder, and Psychotic Disorders) using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); PTSD using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995); mild blast related TBI using an instrument newly developed for this study loosely based on existing interviews used in acute rehabilitation settings (e.g., Gioia et al., 2008). [Dr. McDonald, Dr. Cifu, Brian Bush, and Dr. Walker]

   Accomplished.

2. Collect these interview measures in the subsequent approximately 200 subjects entering Phase 2. [Dr. McDonald, Dr. Walker, Trained Research Assistants]

   Phase-II activity (see D1 above). Structured interviews commenced in Year-Two and we **completed them on 106 subjects**.

3. Analyze findings and implications for the primary analyses described in Tasks 2 and 3. [Dr. Sima, Dr Walker, and all investigators]

   3a. *Blast mTBI structured interview.*

   Based on earlier analyses (full published manuscript in Appendix) showing inconsistencies among the TBI items of our questionnaire (W. Walker et al., 2012), we determined that a structured interview for blast mTBI should be developed and tested. After developing, implementing and collecting data with this new instrument, we found that inter-rater reliability of mTBI diagnosis interpretation was below desired. Therefore we developed an algorithm

from the fully structured portion of the interview to match the physician majority rating. In a second smaller sample we showed almost perfect agreement between the algorithm and physician majority rating. Detailed information on interview development and reliability can be found in the accepted manuscript in the Appendix (W. C. Walker et al., IN PRESS).

After the above-noted successful preliminary validation of our novel interview algorithm, we remained concern over the validity of using the questionnaire items to determine mTBI status among the non-interviewed participants who constituted about one half of the sample. Using questionnaire item responses from the 106 interviewed participants, different questionnaire algorithm combinations were trialed with the goal of maximizing agreement between it and the gold-standard interview diagnosis. An algorithm was identified from the alteration of consciousness items of the questionnaire that gave the peak kappa (k = 0.59, 91% correctly classified) versus the interview diagnosis. Using this algorithm we then extrapolated the mTBI diagnoses for the non-interviewed participants so that the entire dataset could be analyzed with respect to blast mTBI diagnosis. Further, based on our clinical experience and supportive data from athletic mTBI literature, we assumed that those having mTBI with PTA were of a more severe grade and would be most likely to experience long-term impairment. So using interview and BESQ data, we also categorized the participants having blast mTBI as either with PTA or without PTA.

3b. *PTSD structured interview.*

In a previously noted and recently accepted manuscript found in the Appendix, we assessed the diagnostic accuracy of the PCL questionnaire in relation to PTSD diagnosis from structured interview (W. C. Walker et al., IN PRESS). We found that PCL >= 58 best defined a PTSD diagnosis because this cut-point gave the peak kappa value (k= 0.54, 81% correct classification rate) versus the structured interview among the 107 interviewed participants. This cut-point is higher than conventional and is indicative of a large amount of post-deployment stress symptoms in this population even in the absence of clinical PTSD. Using this cut-point, we were able to make valid PTSD diagnosis classifications for the non-interviewed participants.

4c. *Other mood and anxiety disorder diagnoses.*

Analyses of this data were just completed and are contained in a nearly completed manuscript that will be submitted for publication shortly. A brief synopsis follows:

Overall, over half (N=55, 51%) of the participants had an active anxiety disorder and 33 participants (31%) had a mood disorder at the time of DSM IV interview. Fifteen percent (N=15) of the participants were diagnosed with bipolar disorder at the time of the interview and an additional 11 (10%) had depression. Of the anxiety disorders, participants were most likely to have PTSD (N=29, 2%) and agoraphobia (N=19, 18%) at the time of interview.

Neither the blast mTBI category (P=0.747) nor the number of blasts (0.880) were found to be significantly related to the occurrence of a mood disorder. For anxiety disorders, there was an association with the number of blasts experienced by the participant (P=0.003), but there was not an association with blast mTBI category. Specifically, having 5 or more blast experiences resulted in 5.25 (95% CI: 2.00, 13.8) times increase in the odds of being diagnosed with an anxiety disorder. No other pairwise differences were significant at the 0.05 level.

E. *Task 5:* Determine the trajectory of symptoms and social/vocational functioning in PCS after blast related MTBI (Study Phase-III). Timeline: Gradual accrual into Phase 2 of 225

total subjects over 4 years (25 subjects by end Year 1, 125 subjects by end Year 2, 225 subjects by end Year 3). Responsible personnel: listed below for each subtask [ ].

1. On over 232 returnees (consecutive Phase-I enrollments described in Task 1 & 2), collect follow-up longitudinal data (6 months, and one year) on phase-I current-state measures, AND collect complete longitudinal outcome data (6 months and one year) using standardized and validated TBI specific outcome measures including: Extended Glasgow Outcome Scale (GOS-E) (Wilson et al, 1998) (global outcome), Mayo-Portland Adaptability Inventory-4 (MPAI-4)(Malec, 2004) (ability, participation, adjustment), and the Satisfaction With Life Scale (SWLS) (Diener et al, 1985) (quality of life). [scheduling: Research Assistants. Telephonic or in-person data collection: Research Assistants]

We completed 6-month evaluations on **147** participants and 12-month evaluations on **155** participants.

2. Describe the trajectory of symptoms and social/vocational functioning among returnees with PCS after blast-related MTBI. [Analysis by all key investigators]

Symptom and outcome variables were assessed longitudinally using a linear mixed-effect model. Symptom measures included PTSD (PCL), depression (CESD), post-concussive (RPQ), and pain (McGill). Outcome measures included global (GOSE), life satisfaction (SWLS), and social/occupational participation (Mayo). The results are displayed in Tables 4 & 5 of the supporting data section VIII F. None of the variables demonstrated any significant change at 6 or 12 months compared to initial assessment ($P>0.05$). The mean GOSE of 6.4 at both time points corresponds to between moderate disability upper (6) and good recovery lower (7). The cohort's MPAI-4 participation index scores were mainly in the "mild limitation" range (T-scores between 30 and 40) when compared to a national database of predominantly moderate-severe TBI patients.

3. Conduct statistical analysis using repeated measures mixed-models for analysis of outcomes over time (baseline, 6 months, and one year). [Statistics: Dr Sima, Interpretation: All key investigators]

Statistical analysis of the Rivermead post-concussive syndrome questionnaire (RPQ) was undertaken to determine if changes from baseline were able to be predicted from any blast related characteristics using separate repeated measures mixed model for each characteristic. The RPQ is a score in the range [0,64] with higher values indicating worse symptoms. The results are displayed in supporting data section VIII F, Table 6. None of the included factors was predictive of change in RPQ over time ($P>0.05$, "Change" column of Table 6). However, several of these characteristics are related to the RPQ scores averaged across time ($P<0.05$, "combined" column of Table 6). Specifically, participants with PTSD diagnosed or moderate-severe depression symptoms had worse RPQ scores than those that had no PTSD or none-mild depression symptoms respectively. Participants with either 2 or more blasts mTBIs had worse RPQ scores than those that did not have any blast mTBI or just 1 blast mTBI. No other blast characteristics were significantly related to the RPQ scores.

F. Task 6 – Objective: Disseminate Findings:

1. Disseminate results via publication in peer reviewed journals. *[*All key investigators coordinated/led by Dr. Walker]

a. Publications (print or electronic ahead of print) in peer-reviewed journals to date:

- Stratton KJ, Clark SL, Hawn SE, Amstadter AB, Cifu DX, Walker WC. Longitudinal Interactions Of Pain Symptoms And Posttraumatic Stress Disorder In U.S. Military Service Members Following Blast Exposure. *J Pain*.2014 Jul 16. [Epub ahead of print]
- Franke LM, Czarnota, J.N, Ketchum JM, Walker WC. Factor Analysis of persistent postconcussive symptoms within a military sample with blast exposure. *J Head Trauma Rehabil*. 2014 May 6. [Epub ahead of print]
- Walker, W., Nichols, M., McDonald, S., Ketchum, J., & Cifu, D. The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome. *J Head Trauma Rehabil.* 2013 Jan;28(1):68-76.

b. In-Press publications (accepted in peer-reviewed journal, publication pending):

- Walker WC, Cifu DX, Hudak A, Goldberg G, Kunz R, Sima A. Diagnosis of Mild Traumatic Brain Injury after military blast: physician agreement and validity of novel structured interview. Accepted in: *J Neurotrauma*.
- Walker WC, McDonald SD, Franke LM. Ketchum The diagnostic accuracy of the PTSD Checklist in blast-exposed military personnel. ACCEPTED in: *J Rehabil Res & Devel Rehabil*.
- Stratton KJ, Hawn SE, Amstadter AB, Cifu DX, Walker WC. Correlates of Chronic Pain Among Iraqi and Afghanistan Military Personnel following Combat-related Blast Exposure. Accepted in: *J Rehabil Res & Devel Rehabil*.

c. Submitted for publication in peer-reviewed journal:

- Wares JR, Hoke K, Walker WC, Franke LM, Cifu DX, Carne W, Ford-Smith C. Characterizing the effects of mTBI and PTSD on balance in blast-exposed Service Members and Veterans using computerized posturography. Submitted to *J Head Trauma Rehabil*.

2. *Present at professional meetings to reach the variety of practitioners treating TBI and blast injured patients* [All key investigators coordinated/led by Dr. Walker].

National Presentations to date: (accomplishments this reporting quarter **in bold**)

- Oral Symposium presentation, Military Health Research Forum, Kansas City, MI, Sept 1, 2009.
- Poster presentation, Military Health Research Forum, Kansas City, MI, Sept 2, 2009.
- Kelly, N.R., McDonald, S., Sima, J.M., Nichols, M., & Walker, W. (2011, June 13-15). Balance and cognitive functioning: Associations following blast exposure. Poster presented at the 3rd Federal TBI Interagency Conference in Washington, D.C.
- Walker WC, Nichols M, McDonald S, Cifu DX, Sima, J. The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome. Amer Academy Phys Med Rehabil Annual Assembly, November 2011, Orlando, FL. (Poster Hall presentation plus separate Oral Platform session presentation for "Neurologic Best Research Presentations" awardees)
- Franke LM, Sima JM, Walker WC. Factor Analysis of the Rivermead Postconcussion Questionnaire Following Blast Exposure. Poster presentation at American Congress of Rehabilitation Medicine and American Society of Neurorehabilitation (ACRM-ASNR) Annual Conference, Oct 9-13, 2012, Vancouver BC, Canada.
- Hawn S., Kelcey J. Stratton, Clark SL, Amstadter AB, Cifu DX, Walker WC. Longitudinal Trajectories Of Pain Symptoms And Posttraumatic Stress Disorder In US Military

Service Members Following Combat Exposure. VCU Annual Pain Management & Spine Symposium 2013.

- Walker WC, McDonald SD, Franke LM, Lewis TL. The diagnostic accuracy of the Posttraumatic Stress Disorder Checklist in blast-exposed military personnel. Accepted to present at National Capital Area TBI Research Symposium, March 3-4, Bethesda, MD (note: scheduled for March 3 but Symposium cancelled for this day due to inclement weather).
- Walker WC, Sima A, Cifu DX, et al. Structured interview for Mild TBI after military blast: interrater agreement and development of diagnostic algorithm. Accepted for poster presentation at American Congress of Rehabilitation Medicine (ACRM) 91st Annual Conference, Oct 7-11, 2014, Toronto, ON, Canada.

III. KEY RESEARCH ACCOMPLISHMENTS:

- See previous task (Task 6) for publications and presentations accomplished to date.
- Developed structured interview for the post-acute detection/diagnosis of mild TBI.

IV. REPORTABLE OUTCOMES:

See IIIF, Task 6, dissemination.

V. CONCLUSION:

This study provides important descriptive information on post-acute outcomes after military blast exposure during OEF/OIF/OND deployment. Symptom severity including PCS, pain, and depression are generally high in this population partly due to a high prevalence of PTSD. PCS symptom severity is probably influenced by blast mTBI but further study is needed to substantiate this link. Unfortunately, symptoms present at around one year after exposure do not dissipate over the ensuing year; suggesting additional treatments are needed. For many, global outcome and social-occupational functioning is in the range expected for more severe brain injuries. We found evidence of cognitive and postural impairments that appear to be viable treatment targets. Those having sustained blast mTBI with PTA are especially to cognitive and postural deficits. Alterations on QEEG power spectrum were also associated with blast mTBI grade. Thus, we found evidence for converging physiologic and performance data suggesting residual persisting effects of blast mTBI.

VI. REFERENCES:

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., et al. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8*, 75-90.

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Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33.

VII. APPENDICES (separate pdf attachments):

APPENDIX # 1: Manuscripts published in peer-reviewed scientific journals

APPENDIX #2: Manuscripts in press; accepted by peer-reviewed scientific journals

APPENDIX #3: Manuscripts submitted to peer-reviewed scientific journals

VIII. SUPPORTING DATA

A. Participant Demographics

Table 1. Demographic Summary Sheet (n=216)

Variable	Mean	SD	Range
Age, years	27.4	7.6	19 – 60
	Percent		
Sex			
Male	96.8		
Female	3.2		
Marital Status			
Married	47.2		
Divorced	8.3		
Single	44.4		
Race			
Caucasian	78.2		
African American	15.3		
Other[1]	6.5		
Ethnicity			
Hispanic	10.2		
Non-Hispanic	89.8		
Highest Level of Education			
Non-High School	0.9		
High School Graduate	50.9		
Some College	35.2		
College Graduate	11.6		
Post-Graduate Degree	1.4		
Prior Deployment Status			
Active Duty	76.4		
Selective Reserves – National Guard	13.9		
Select Reserves – Reserves	6.5		
Ready Reserves	1.9		
Civilian Government Employee	0.9		
Other (Contractor)	0.5		

[1] Other Race includes: 1 Black/White, 6 Hispanic, 3 Latino, 1 Latino/White, 1 Native American, 1 Native American/Black, 1 White/Asian.

VIII B. Supplemental analyses on relationship between exposure variables and post-concussion syndrome (PCS)

We analyzed the relationship between PCS and several injury variables and the results are displayed in Table 2. Having symptoms consistent with PCS was associated with a greater number of Blast mTBIs as well as having PTSD. There was a trend toward an association between blast mTBI grade and PCS. There was no relationship between self-reported non-blast head injuries or month since worst or most recent blast experience.

Table 2. Relationship between exposure variables and Post-Concussion Syndrome

		PCS		
Measure	**Level**	**Yes**	**No**	***p*-value**
Worst Blast mTBI	High Grade mTBI	88 (81%)	20 (20%)	0.1073
	Low Grade mTBI	52 (76%)	16 (24%)	
	No mTBI	26 (65%)	14 (35%)	
Number of Blast mTBI	0	26 (65%)	14 (35%)	0.0070
	1	70 (72%)	27 (28%)	
	2	44 (94%)	3 (6%)	
	3+	26 (81%)	6 (19%)	
PTSD	Yes	57 (93%)	4 (7%)	0.0003
	No	109 (70%)	46 (30%)	
Any Non-Blast Head Injuries	Yes	67 (76%)	21 (24%)	0.8362
	No	99 (77%)	29 (23%)	
Months Since Worst Blast		17.0 (17.3)	18.5 (18.3)	0.5922
Months Since Most Recent Blast		11.1 (7.7)	13.2 (9.8)	0.1284

Participants who sustained blast mTBI with PTA also had higher mean post-concussive symptom severity on the RPQ compared to those not sustaining mTBI (see Table 3).

Table 3. PCS symptom severity among Blast mTBI groups

Rivermead Questionnaire (RPQ 16item) ; n=216

Worst Blast TBI	Mean	N	Std. Deviation
*mTBI with PTA	31.41	108	12.28
mTBI with**out** PTA	29.07	68	13.02
* Not TBI	24.70	40	13.55

ANOVA between groups F=2.6, p=0.018

*$p < 0.05$ on post-hoc T-test

There were also significant differences between mTBI grade groups in vestibular (p=0.001) and cognitive (p=0.013) symptoms on the RPQ factor scores. For vestibular symptoms, In addition to the mTBI with PTA group being higher than the not mTBI group, post-hoc testing also showed worse symptoms for the mTBI without PTA group compared to the no TBI group (p=0.008). Although the mean RPQ total and factor scores were all nominally higher for mTBI with PTA versus without PTA groups, no difference was statistically significant.

VIII. C. Supplemental Neuropsychological Testing Data

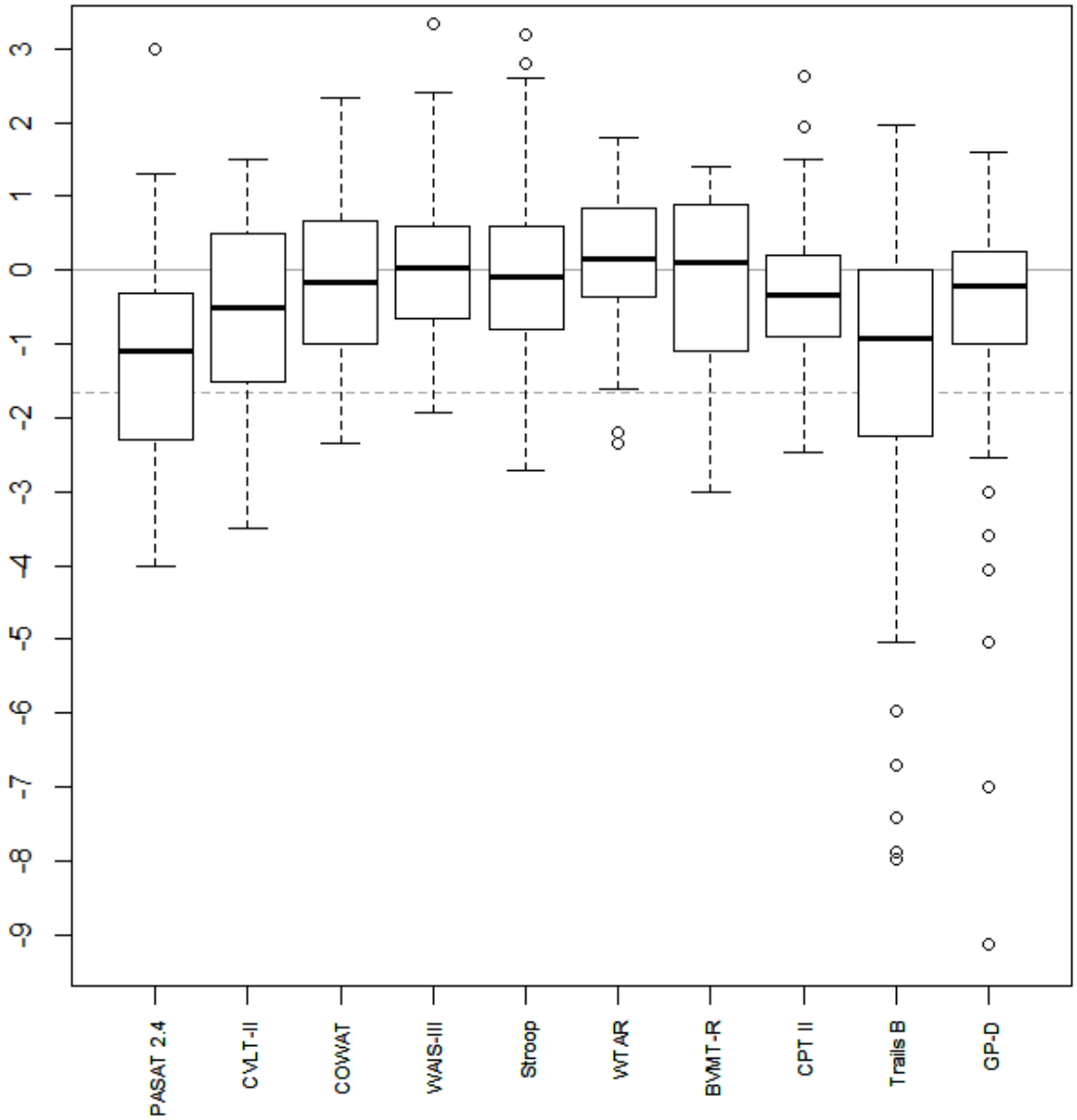

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Figure 1. Summary information for each of the primary neuropsychological measures. Horizontal bars within each box represent the median value. The solid and dashed reference lines represent the normative mean value (Z=0) and the cutoff for classifying a participant as impaired (Z=-1.64 or 5th percentile), respectively. Entire sample completing neuropsychological testing minus 19 participants excluded who failed effort testing (TOMM); n=156.

VIII D. Supplemental Computerized Posturography Data

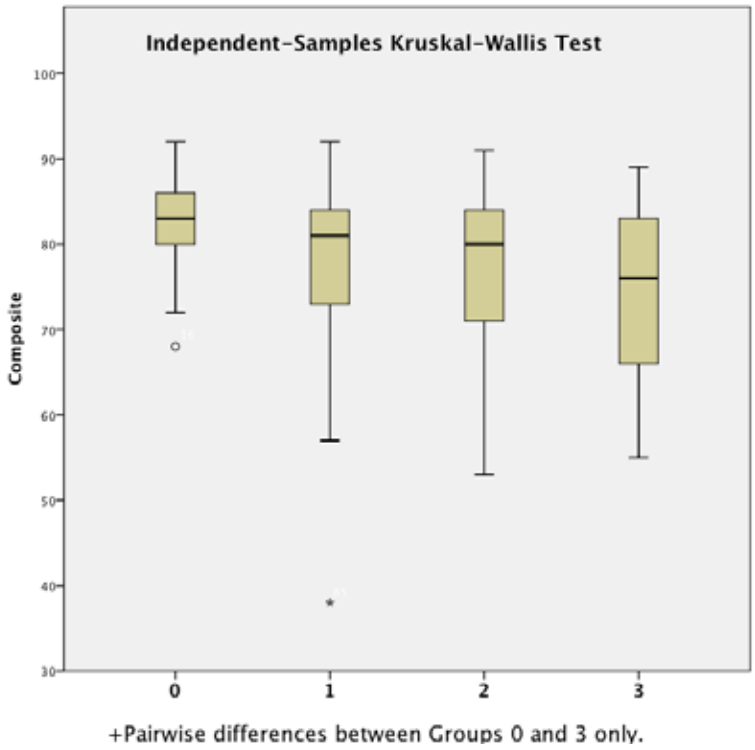

Figure 2: Boxplots of the composite score distributions for Groups 0 (neither diagnosis), 1 (isolated blast mTBI with PTA), 2 (isolated PTSD) 3 (comorbid mTBI and PTSD). Post-hoc tests show Groups 0 and 3 have significantly different medians.

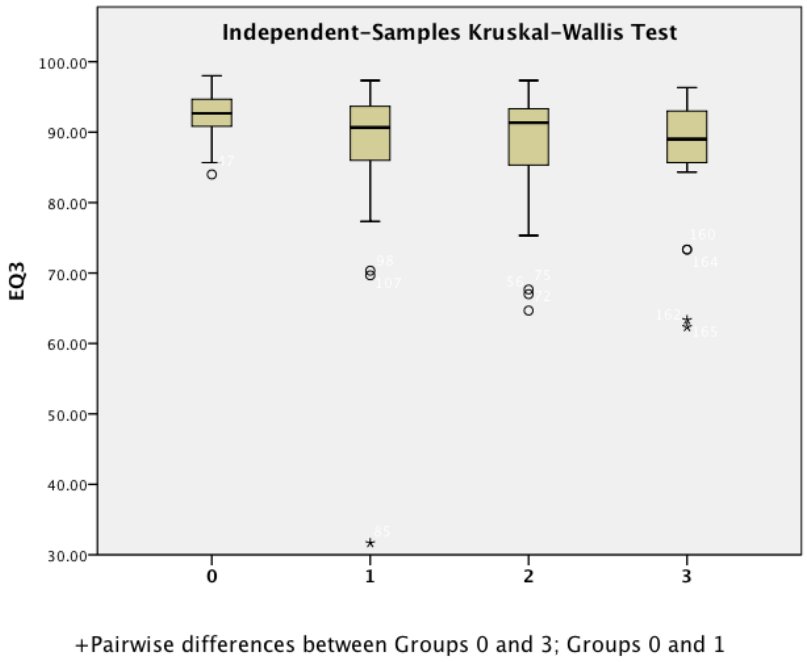

Figure 3: Boxplots of Equilibrium Condition 3 for Groups 0, 1, 2 3 (x-axis). Post-hoc tests show Group 0 (neither blast mTBI with PTA nor PTSD) and 1 (blast mTBI with PTA only) have significantly different medians. Additionally, Groups 0 and 3 have significantly different medians.

VIII E. Supplemental QEEG analyses data

Blast mTBI was associated with increased power in the lower frequencies. These effects were seen across the scalp. The below graphs (Figures 4 and 5) show right and midline frontal sites.

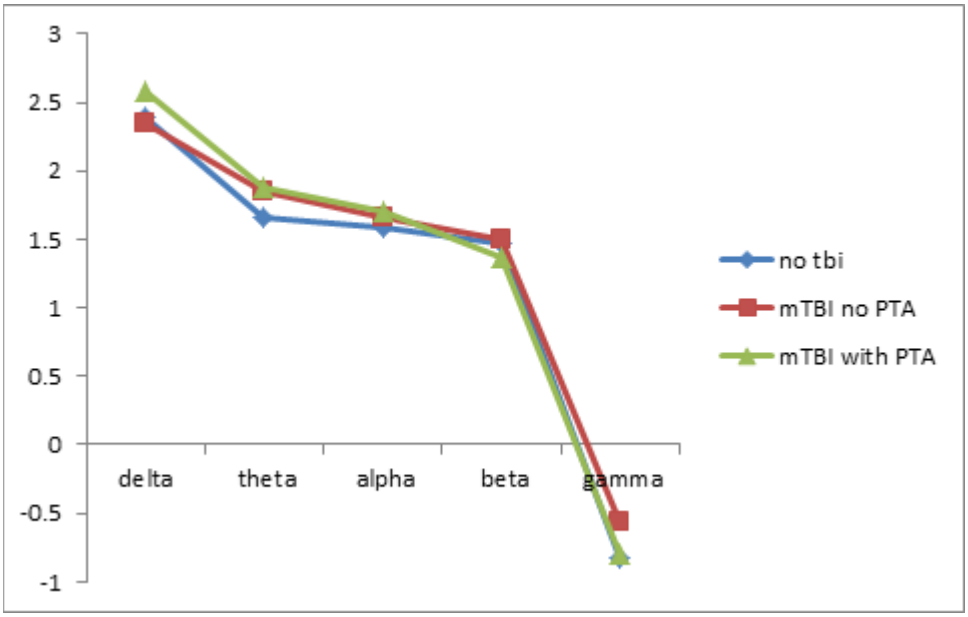

Figure 4. QEEG Power at Right Frontal electrode site across TBI groups

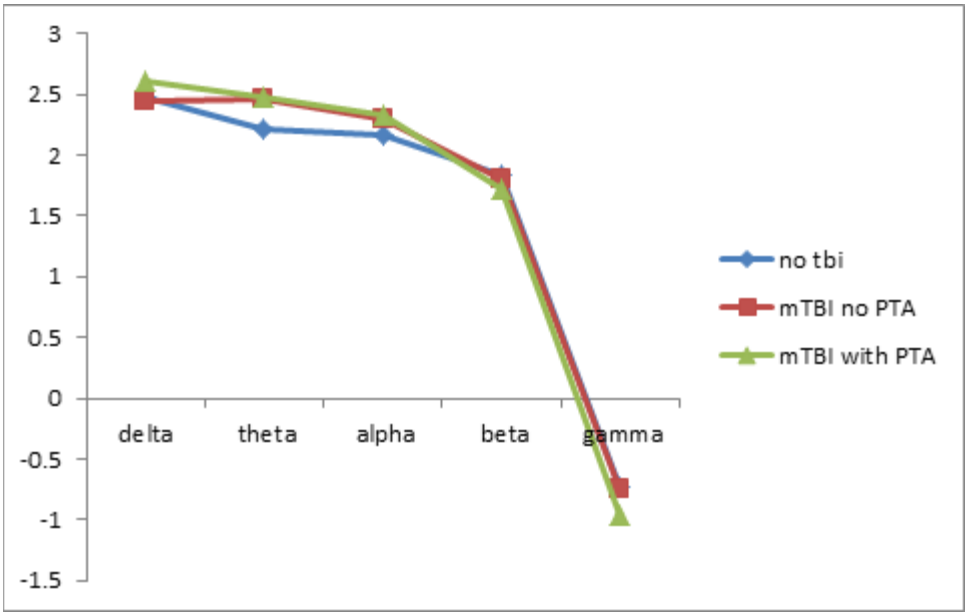

Figure 5. QEEG Power at Frontal Midline electrode site across TBI groups

Interaction at Cz -demonstrates how TBI and PTSD have opposing effects at the lower frequencies. TBI without PTA and no TBI are grouped together here.

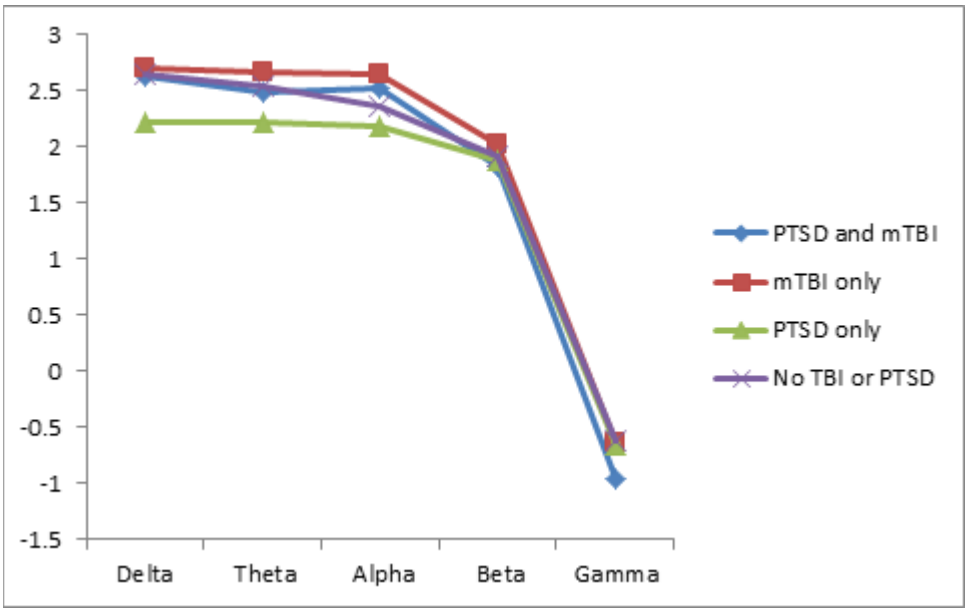

Figure 6. QEEG Power spectrum comparing Blast mTBI and PTSD diagnoses

VIII F. Longitudinal analyses.

Within the entire cohort, none of the symptoms measures improved or worsened during the first year after baseline assessments; which roughly corresponded to on average from year-one to year-two after most recent blast exposure (see Table 4). Similarly, functional and perceived outcomes did not change between 6 months and 12 months after baseline assessments (see Table 5).

Table 4. Symptom measures over time

Measure	Baseline	6-month	12-month	*p*-value
PCL	45.8	46.9	48.0	0.1494
	(43.3, 48.3)	(44.3, 49.5)	(46.0, 50.0)	
CESD	17.8	17.7	18.0	0.9378
	(16.4, 119.2)	(15.8, 19.7)	(16.0, 20.0)	
RPQ	29.5	29.7	29.4	0.9664
	(27.7, 31.2)	(27.5, 31.8)	(27.4, 31.4)	
McGill	11.0	11.4	11.8	0.5092
	(9.9, 12.0)	(10.1, 12.7)	(10.4, 13.2)	

Table 5. Outcome measures over time

Measure	Baseline	6-month	12-month	*p*-value
GOSE	-	6.4	6.4	0.9560
		(6.2, 6.7)	(6.2, 6.6)	
SWLS	-	21.0	21.8	0.0804
		(19.8, 22.1)	(20.6, 23.1)	
Mayo	-	6.3	6.0	0.3939
		(5.4, 7.2)	(5.0, 6.9)	

Even though PCS symptom severity (RPQ total) did not change over time within the entire cohort, our earlier analyses showed that baseline RPQ varied across certain groups. So it was possible that within groups, RPQ could change over time in opposing directions and mask any time effect within the entire cohort. Therefore we analyzed the interaction between key baseline prognostic variables and time in relation to RPQ total. These results are displayed in Table 5. The combined average RPQ across time was related to several factors including depression symptoms, PTSD diagnosis, and grade and number of blast mTBI (see Table 5 Average p-value column). However none of these factors was associated with change in RPQ total over time (see Table 5 Change p-value column).

Of note, the nominal mean values of average RPQ scores shows an interesting pattern across the number of blast mTBI groups. There is a progressive increase in symptoms from 0 to 1 to 2 blast mTBIs that then levels off with no further increase from 2 to 3+ blast mTBIs. Additionally, the nominal magnitude of difference is greater from 1 to 2 than from 0 to 1. This may indicate a persisting PCS symptom threshold effect between 1 and 2 blast mTBIs.

Table 6. Influence of baseline factors and time on PCS symptom severity

Baseline Measure	Level	RPQ Averaged across time (0, 6, 12 months)	Average *p*-value	Change *p*-value
Depression Symptoms	None/Mild	25.7 (24.2, 27.4)	<0.0001	0.5079
	Moderate/Severe	35.9 (34.0, 37.8)		
PTSD Diagnosis	Yes	37.2 (35.1, 39.2)	<0.0001	0.8188
	No	26.5 (25.0, 28.0)		
Residual Active PCS	Blast mTBI with PCS	N/A	N/A	0.4561
	Blast mTBI without PCS	N/A		
	No Blast TBI	N/A		
Number of Blasts	1	26.7 (22.9, 30.5)	0.1196	0.9179
	2-4	31.4 (28.8, 34.0)		
	5+	28.9 (26.4, 31.5)		
Worst Blast mTBI Grade	Blast mTBI with PTA	30.9 (28.6, 33.3)	0.0509	0.5642
	Blast mTBI without PTA	29.5 (26.5, 32.5)		
	No Blast TBI	25.4 (21.6, 29.2)		
Number of Blast mTBIs	0	25.4 (21.6, 29.1)	0.0010	0.5551
	1	27.6 (25.1, 30.0)		
	2	33.9 (30.5, 37.4)		
	3+	33.3 (29.2, 37.5)		
Non-blast head Injury	Yes	29.1 (26.5, 31.7)	0.7036	0.5175
	No	29.7 (27.5, 31.9)		

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Identification of Transient Altered Consciousness Induced by Military-Related Blast Exposure and Its Relation to Postconcussion Symptoms

William C. Walker, MD; Scott D. McDonald, PhD; Jessica M. Ketchum, PhD; Michelle Nichols, MSN, RN; David X. Cifu, MD

Background: The ongoing controversy whether mild traumatic brain injury (TBI) can cause chronic sequel is partly due to diagnostic limitations. Diagnosing mild TBI is particularly challenging when assessment is not immediate, and when informed, first responder documentation or witness corroboration is absent. In this common scenario, the diagnosis is made entirely on self-report of an initial period of alteration of consciousness (AOC) associated with a plausible injury mechanism. Yet, there is scant published empirical guidance on methods for accurately detecting historical AOC. **Objectives:** To assess the value that recalled AOC symptoms collected via questionnaire have in evaluating individuals exposed to blast during recent military deployment. More specifically, to analyze the concrete AOC items (those signifying unconsciousness and/or posttraumatic amnesia) for their (1) frequency and distribution of positive versus negative responses, (2) interitem agreement, and (3) relation to current neuropsychiatric symptoms including those consistent with postconcussion syndrome (PCS). **Participants:** Eighty-seven active duty or Veteran subjects who experienced acute effects from a blast within the past 2 years while deployed for Operations Enduring and Iraqi Freedom. **Results:** Twenty-nine participants (33.3%) responded positively to at least 1 of 3 concrete AOC items: gap in memory (17.2%), memory not continuous (13.8%), and/or told by observer they had loss of consciousness (20.7%). Alteration of consciousness items were associated with but nondiscriminate of current symptom distress on standardized measures of PCS (Rivermead Postconcussion Symptom Questionnaire), posttraumatic stress disorder (PTSD; PTSD Checklist), depression (Centers for Epidemiological Studies Depression Scale), and pain (Short Form McGill Pain Questionnaire). **Conclusions:** The positive association between subjects' questionnaire-based AOC item responses and current symptom complex measures suggests that mild TBI has a role in the development of chronic neuropsychiatric symptoms after blast exposure. The lack of symptom- complex discrimination, and the inconsistencies found in subjects' item responses suggest that a structured interview may improve postacute diagnostic specificity for mild TBI. **Key words:** *brain injury*, *concussion*, *explosive blast*, *military injury*, *questionnaire*

TRAUMATIC BRAIN INJURY (TBI) is a potentially debilitating condition that can be associated with difficulties in daily functioning and poor health.[1] It has been called as the "signature wound" of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF). An estimated 19% of military personnel sustain a TBI during deployment.[2] Although nearly 80% of these are of mild severity,[3] up to 20% of persons with mild TBI are likely to develop Postconcussion Syndrome (PCS), a condition of chronic or even permanent symptoms that may include cognitive impairments and detrimental effects on psychosocial functioning.[4,5] Therefore, both the Department of Veterans Affairs (VA) and the

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The authors declare no conflicts of interest.

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Department of Defense (DoD) have made early identification of, accurate diagnosis of, and access to effective treatments for, the effects of TBI a research priority. However, primary research efforts to improve the diagnostic accuracy of TBI have concentrated on the search for biomarker and imaging substrates, with relatively less attention placed on refinement of the criterion standard clinical assessment.

The clinical hallmark of diffuse axonal injury from TBI is an initial period of alteration of consciousness (AOC) with or without frank loss of consciousness (LOC).[6] Empirical research clearly shows that TBI outcomes become progressively worse the longer the AOC period persists.[7] Even in samples of sport-related mild TBI, the presence of AOC as expressed by posttraumatic amnesia (PTA) is a strong predictor of poorer outcome.[8] When TBI is severe, the period of AOC persists for longer than 1 week and typically includes an initial period of LOC or coma. Although accompanying drug or alcohol toxicity or cardiopulmonary failure may confound assessment, severe TBI rarely poses a diagnostic dilemma, even when neuroimaging is unrevealing or absent. However, in cases of mild TBI or concussion, which account for approximately 80% of all civilian TBIs and may represent even more of the total combat-related injuries, determining the presence of an initial AOC period can be quite challenging, and acute neuroimaging is typically normal or absent.

The Centers for Disease Control and Prevention Mild TBI Work Group defines mild TBI as an injury to the head resulting from blunt trauma or acceleration or deceleration forces, with one or more of the following conditions attributable to the head injury: (1) any period of observed or self-reported transient confusion, disorientation, or impaired consciousness; (2) any period of observed or self-reported dysfunction of memory (amnesia) around the time of injury lasting 24 hours or less; (3) any period of observed or self-reported LOC lasting 30 minutes or less; and (4) acute seizure after injury to the head.[9] These guidelines also stipulate that postinjury symptoms (eg, headache, dizziness, irritability, fatigue, or poor concentration) can be used to support, but cannot be used to make, a diagnosis of mild TBI in adults. Therefore, in the absence of seizure, determining that a period of AOC has occurred is essential to making the diagnosis of mild TBI in the context of a known injury force such as a blast event. To confound this determination, AOC may be as brief as minutes or seconds and there is usually no initial period of LOC.

The earlier patients with suspected mild TBI are evaluated after injury, the more likely that signs of initial AOC will be present to aid in verifying the diagnosis. For example, in the highly competitive sports setting, medical personnel are generally available to provide immediate assessment.[10] Furthermore, validated, structured symptom measures and mental status examinations exist to assist the acute diagnosis.[11] However, in most settings, including community-level athletics, there is usually a time lag prior to formal acute medical evaluation. During this time, the AOC period often resolves, and the diagnosis of mild TBI may be missed. For example, in a recent study of emergency department patients, study personnel identified more than twice as many patients with mild TBI than those who received a documented diagnosis.[12] When patients are screened for TBI much further postacutely, as with the existing postdeployment military assessments or the new Veteran screening evaluations, mild TBI is especially difficult to diagnose. In the absence of first responder documentation or witness corroboration, the diagnosis must be made entirely from recalled history. The examiner must determine the existence or nonexistence of an initial AOC period solely from the patient's self-reported recall.

Despite both the US DoD's and Veterans Health Administration's increased focus on identification of brain injury during recent and past military service, there are limited published data reporting the validity or reliability of diagnostic questionnaires or interviews after mild TBI. Existing research also provides scant psychometric data on postacute diagnostic tools for mild TBI, such as reliably eliciting self-report of an earlier AOC experience. These issues and factors highlight the significance of more clearly understanding the value of postacute assessment in determining a mild TBI diagnosis.

The Ohio State University TBI Identification Method (OSU TBI-ID) is a structured interview designed for retrospective identification of TBI.[13] Interrater reliability correlations among trained research assistants were high ($r > 0.9$) for identifying TBI in a substance abuse population when the case definition was "knocked out or unconscious." Correlations were also high ($r > 0.92$) for "number of effects" experienced, but TBI diagnosis was not made from these items alone; hence, no reliability for TBI without LOC was reported. In predictive validity assessment, neither severity of injury construct, nor time since injury construct, nor early symptoms experienced, nor greater number of TBIs were associated with greater present self-report of cognitive problems or objective problems in memory, attention, or abstraction. Test-retest reliability of the OSU TBI-ID was assessed in a separate prisoner sample and found to be fair for the number of initial symptoms ($r = 0.74$) and number of initial functional effects ($r = 0.72$).[14] However, reliability of individual symptoms or effects and reliability of profiles consistent with TBI were not assessed.

The Brief Traumatic Brain Injury Screen (BTBIS) is a self-report tool for "probable" TBI and problems and symptoms that may be associated with TBI.[15] The BTBIS was compared to a presumed criterion standard, semistructured interview, in a military sample. This

interview consisted of a series of primarily open-ended questions with vetting of responses left to judgment of the interviewer, either a Masters' level psychologist or trained staff member. Of the BTBIS positive soldiers, 85% were positive for TBI on interview, yielding a 15% false-positive rate. False-negatives were not sought, because those who screened negative were not contacted for interview. The Traumatic Brain Injury Questionnaire is a semistructured interview with 12 closed-ended (Y/N) response items assessing for a possible TBI incident, followed by open-ended interview of the incident(s) identified. Test-retest reliability showed a κ statistic of 0.56 (moderate agreement), with trained research assistants conducting the interviews in a prison offender sample.[16] However, open-ended question responses were not reported and interrater reliability was not assessed. Thus, preliminary psychometric data are mixed, and the specificity and sensitivity of these interview and questionnaire tools for detecting mild TBI retrospectively is unknown.

The current study sought to further analyze methods of incorporating AOC symptoms into a standardized, retrospective symptom assessment for diagnosing mild TBI and TBI sequelae. We specifically focused on the most concrete of the self-report AOC symptoms contained in the Centers for Disease Control and Prevention diagnostic criteria for mild TBI, observed LOC and amnesia immediately before or after the time of injury. During the initial AOC period caused by TBI, the brain has impaired formation of new memories, such that this period is also termed PTA.[17] The period of PTA may or may not include a briefer initial LOC period. After resolution of PTA, this time period is "forgotten" (or was never "remembered") and thus offers a concrete construct for the examiner to probe with interview questioning.[18] In severe TBI, at least one study has shown a strong correlation between medical record documentation gathered and interview-determined duration of PTA.[19] However, the reliability and validity of this retrospective AOC/PTA measurement has not been well tested in mild TBI, where the duration of PTA cannot be counted in days and may be as brief as 1 minute or less. Mild TBI screening tools, such as those used in the VA Medical Center system of care, typically include an item for detecting PTA using the term "memory gap." However, this term is somewhat abstract, and its sensitivity and specificity for detecting PTA are unknown. Diagnostic interviews typically use an inverse construct, querying the patient on whether he/she personally remembers "everything" from the event and its immediate aftermath.

In this study, we analyzed questionnaire responses on recalled AOC/PTA symptoms among individuals who had military blast-exposure in the past 2 years. This study is part of a larger ongoing epidemiologic study of OEF/OIF Service Members and Veterans who had a blast exposure during a recent OEF/OIF tour. Among other data, this study is examining self-reported symptoms of AOC/PTA immediately after the blast. We utilized both the standard (memory gap) and inverse (continuous memory) method of questioning patients about the presence or absence of PTA. In addition to describing the frequency and distribution of positive versus negative responses, specific objectives and hypotheses of this study were as follows:

Objective 1: To assess the agreement among the 3 concrete AOC period item responses on the Blast Experience Screening Questionnaire (BESQ) that probed for the existence of initial PTA and/or LOC (gap in memory, memory not continuous, and/or told by observer they had loss of consciousness).

Hypotheses for objective 1:

(a) Respondents reporting a gap in memory will have high concordance with those reporting discontinuous memory; and

(b) Respondents reporting LOC will report both a memory gap and discontinuous memory.

Objective 2: To assess the relations among the concrete AOC period item responses and standardized self-report measures of current PCS using the Rivermead Postconcussion Symptom Questionnaire (RPQ),[20] posttraumatic stress disorder (PTSD) using the PTSD Checklist, Civilian Version (PCL-C),[21] depression using the Centers for Epidemiological Studies Depression Scale (CES-D),[22] and pain using the Short Form McGill Pain Questionnaire (SF-MPQ).[23]

Hypothesis for objective 2:

(a) Positive responses to memory gap will be associated with more current symptoms;

(b) Negative responses to continuous memory will be associated with more current symptoms; and

(c) Positive responses to LOC will be associated with more current symptoms.

MATERIALS AND METHODS

Participants

This study sample was derived from the first 89 subjects consented and enrolled in an epidemiological study of blast exposure during OEF/OIF. In the overarching study, eligible Military Service Members and Veterans had a blast experience within the past 2 years while deployed in OEF/OIF. Participants were recruited via letters, advertisements, and from ambulatory healthcare clinics at the Hunter Holmes McGuire VA Medical Center in Richmond, Virginia, Fort Lee Army Base in Prince George County, Virginia, and Quantico Marine Corps Base in Prince William County, Virginia. *Blast experience* was defined as having any of the following symptoms or experiences occurring during or shortly after exposure to blast or explosion: dazed, confused, saw stars, headache,

dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, or medically evacuated. Individuals with severe or moderate TBI were excluded, so participants who may have sustained a TBI during their blast experience would be in the mild TBI category. *Severe or moderate TBI* was defined as more than 24 hours in coma, brain bleeding or blood clot (abnormal brain CT scan), or amnesia for the first 24 or more hours after event. Two individuals were excluded because their self-reported amnesia exceeded 24 hours, yielding a final sample size of 87 participants with blast experiences .that were. absent either moderate or severe TBI. The demographic characteristics of the study sample are displayed in Table 1. Participants were evaluated at a median of 15.1 months (interquartile range [IQR] = 10.1–24.4) after their worst blast experience and 12.9 months (IQR = 8.0–19.9) after the most recent of their 3 reported worst blast experiences.

TABLE 1 *Demographic characteristics of sample (n = 87)*

Variable	Median	IQR
Age, y	27.0	24-36
Months since most worst blast exposure	15.1	10.1-24.4
Months since most recent blast exposure	12.9	8.0-19.9
	Count	**Percent**
Sex		
Male	82	94.3
Female	5	5.7
Marital status		
Married	39	44.8
Divorced	10	11.5
Single	38	43.7
Race		
Caucasian	58	67.4
African American	22	25.6
Other	6	7.0
Ethnicity		
Hispanic	8	9.4
Non-Hispanic	77	90.6
Highest level of education		
High school graduate	34	39.1
Some college	40	46.0
College graduate	12	13.8
Postgraduate degree	1	1.1
Prior deployment status		
Active duty	53	60.9
Selective reserves—national guard	23	26.4
Selective reserves—reserve	7	8.0
Ready reserves	3	3.4
Civilian government employee	1	1.1

Abbreviation: IQR, interquartile range.

Procedure

All participants completed a series of self-report questionnaires. Although many were enrolled at clinics, the research evaluations were separate from clinical care or compensation and pension processes. Research staff supervised completion of all the questionnaires and provided additional instructions as needed.

Measures

Participants were queried on their traumatic blast experience(s) via the BESQ that was developed for the larger epidemiologic study. The BESQ was adapted from the Walter Reed Army Medical Center Blast Injury Questionnaire (WRAMC BIQ), described by Scherer et al[24] in a study of blast-related otovestibular impairments. The WRAMC BIQ screens patients for previously unreported, blast-related pathologic conditions via 19 questions regarding the blast and pre- and postblast otologic symptoms including the presence of visual disturbances, headaches, dizziness, or hearing loss, distance from the blast, and degree of cover. The BESQ asked for information on up to 3 separate blast events, focused on symptoms immediately after the blast exposure, and added items on AOC. The items of BESQ that most concretely probed for recall of time period of AOC immediately after their worst blast experience were extracted for the current study. Specifically, subjects were instructed to respond either yes or no to the following questions: "To your best recollection, did you experience a memory gap during or right after the blast?" and "Did an observer report your losing consciousness (knocked out)?" Subjects were also asked to tell "Not counting normal sleep time do you personally remember the blast and all time immediately before and after?" and to choose between yes and no with qualifiers: "Yes, my memory for the experience is continuous (may have fuzzy parts)" or "No, I have no memory at all for some period of time (whether brief or long) during, immediately before, or immediately after the blast." Subjects also completed standardized, self-report measures of current PCS via the RPQ, PTSD via the PCL–nonspecific version, depression via the CES-D, and Pain via the SF-MPQ. The RPQ is a 16-item self-report measure of the presence and severity of the 16 postconcussion symptoms most commonly reported in the literature. The scale compares any current symptoms to preinjury levels to account for potential symptom exacerbation due to TBI. The RPQ has high test-retest and interrater reliability and adequate external construct validity.[20,25] The PCL-C is

a 17-item self-report measure that evaluates symptoms of PTSD using a 5-point Likert-type scale. The PCL-C has good psychometric properties across various trauma populations.[26,27] The CES-D is a 20-item instrument using a 4-point Likert scale, which was developed by the National Institute of Mental Health to detect major or clinical depression, and it has more than 40 years of clinical and research application.[22] The MPQ-SF is a self-rating of 15 words describing the "quality" of pain from 11 Sensory and 4 Affective items using not present (0), or if it is present, rate it as "mild (1), moderate (2), or severe (3)."[23]

Statistical analyses

Descriptive statistics, including means, standard deviations, frequency counts, and percentages, were used to summarize the continuous and categorical variables. The simple κ coefficient and associated confidence interval assessed the agreement between the 2 amnesia item responses. Two-sample t tests and analysis of variance (ANOVA) were used to test for differences in current PCS, pain, PTSD, and depression symptoms for 2 and 3 group comparisons, respectively. A significance level of $\alpha = 0.05$ was used for all tests, and corrections were not made for multiple comparisons, given the exploratory nature of this study.

RESULTS

Fifteen participants (17.2%) reported a memory gap during or right after the blast, 12 (13.8%) reported not having continuous memory for the blast and the time immediately before and after, and 18 (20.7%) reported an observed LOC. A total of 29 participants (33.3%) responded positively to at least 1 of the 3 items (memory gap, discontinuous memory, and observed LOC) that probed for AOC after blast exposure. The overlap among the positive items reported by these 29 participants is shown diagrammatically in Figure 1. Overall, 6 of 87 (5.7%) reported all 3 (memory gap, LOC, and discontinuous memory), while 58 people (66.7%) reported none.

The pairwise relations between AOC items of positive versus negative responses are displayed in Table 2. There was significant agreement between the 2 amnesia measures ($\kappa = 0.52$, 95% confidence interval = 0.27, 0.77). The concordance between these measures was high, with 8 participants (9.2%) endorsing both amnesia items and 68 (78.2%) endorsing neither, with discordance in the remaining 11 participants (12.6%). Because amnesia can occur without LOC, an agreement coefficient could not be calculated between observed LOC and either amnesia item. However, there were discordant responses among 11 participants (12.6%) who reported LOC with continuous memory and 11 participants (12.6%) who reported LOC without memory gap.

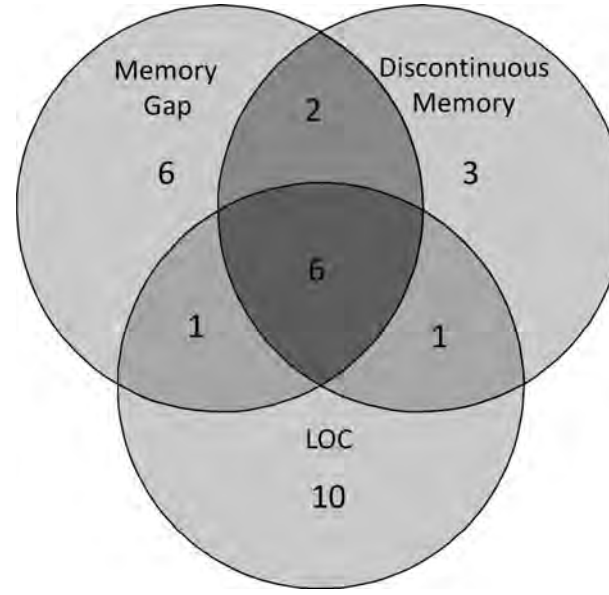

Figure 1. Positive item overlap for the 29 participants endorsing at least one AOC Item.

For positive versus negative responses to each AOC item, t tests were performed to compare measures of current PCS, PTSD, pain, and depression (Table 3). For all 3 items, pain was significantly greater when AOC was reported. Postconcussion syndrome symptoms were significantly greater for those reporting observed LOC, and nominally, although not significantly for the sample size, greater for those endorsing a memory gap or discontinuous memory. Depression symptoms and PTSD symptoms were significantly more severe for those reporting a memory gap and those reporting discontinuous memory. For those reporting observed LOC, depression and PTSD symptoms trended more severe but were not statistically significant.

Lastly, responses from all 3 AOC item responses were combined to create a categorical index of 3 potential diagnostic groups of mild TBI: definite/probable TBI (2 or 3 positive AOC items), possible TBI (1 positive AOC item), and no evidence of TBI (all 3 AOC items negative). Using this scheme, 10 participants (11.5%) had definite/probable TBI, 19 (21.8%) had possible TBI, and 58 (66.7%) had no evidence for TBI. ANOVA tests were performed to compare measures of current PCS, PTSD, pain, and depression among the 3 groups (see Table 4). Overall, there were significant group differences in PCS symptoms ($P = .0267$), pain ($P = .0003$), PTSD severity scores ($P = .0204$), and depression severity scores ($P = .0125$). More specifically, the definite/probable and possible TBI groups both had significantly more severe PCS, pain, and depression symptoms than the group with no evidence of TBI. Furthermore,

TABLE 2 *Pairwise cross-tabulations of gap in memory and continuous memory (no gap), endorsing LOC and continuous memory, and endorsing LOC and memory gap*

	Continuous Memory		
Memory Gap	**No**	**Yes**	**Total**
Yes	8 (9.2%)	7 (8.0%)	15 (17.2%)
No	4 (4.6%)	68 (78.2%)	72 (82.8%)
Total	12 (13.8%)	75 (86.2%)	87
	LOC		
Continuous Memory	**Yes**	**No**	**Total**
No	7 (8.0%)	5 (5.7%)	12 (13.8%)
Yes	11 (12.6%)	64 (73.6%)	75 (86.2%)
Total	18 (20.7%)	69 (79.3%)	87
	LOC		
Memory Gap	**Yes**	**No**	**Total**
Yes	7 (8.0%)	8 (9.2%)	15 (17.2%)
No	11 (12.6%)	61 (70.1%)	72 (82.8%)
Total	18 (20.7%)	69 (79.3%)	87

the definite/probable group had significantly greater PTSD symptom severity than those with no evidence of TBI.

DISCUSSION

The questionnaire-based amnesia items analyzed in this study, memory gap and lack of continuous memory, probed for concrete historical evidence of event-related transient AOC immediately after blast exposure. While agreement on these 2 items was high, it is noteworthy that a number of participants (12.6%) gave discordant responses. These instances of reporting memory gap but also continuous memory, or discontinuous memory with no memory gap, may represent inaccurate recall, "fuzzy" memory periods, misinterpretation of the questionnaire item(s), or symptom "magnification." These findings demonstrate the importance of utilizing multiple approaches when assessing for symptoms of previously experienced altered consciousness, which patients may recollect or interpret differently. Regardless, each of the blast-related amnesia items showed a significant relation with current symptom distress. Those who endorsed either amnesia item either had significantly or nominally higher scores on measures of current PCS, PTSD, depression, and pain, compared to those who gave a negative response. Thus, both items appear to have value in the clinical evaluative process.

Assessing agreement between LOC and the 2 amnesia items was more difficult. Loss of consciousness cannot be "remembered" and hence must be accompanied by amnesia; however, amnesia may or may not be accompanied by LOC. Given this, there was true discordance in those who reported either continuous memory (12.6%) or no memory gap (12.6%), despite reporting an observed LOC. Nonetheless, those endorsing an observed LOC had significantly higher scores on measures of current PCS and pain than those who had a negative response. So, as with both amnesia items, the LOC item was also associated with current symptom distress and seemingly of value in the evaluative process.

It should be noted that our LOC item differed slightly from those used in most prior investigations, including Hoge et al,[28] in that it specifically queried for "observed" LOC. We utilized that format to minimize false-positive LOC responses, wherein a nonremembered experience (amnesic period) might be reported as an unconscious experience; either by the individual assuming that they must have been unconscious, because they could not remember the experience, and/or by symptom magnification. So, those who reported an amnesic period without LOC should be considered concordant because it is a physiologically feasible and common scenario.

While the self-reported evidence of AOC in this study is associated with greater symptom distress, it also appears to lack discrimination for residual diagnosis (ie, PCS vs PTSD vs depression vs chronic pain), at least among the symptom diagnosis tools employed. The overlapping symptoms among the symptom diagnosis tools used may account for their high degree of covariance. Postconcussion syndrome and PTSD, in particular, have a number of common symptoms, and both have been linked to depression and chronic pain. Once a larger sample size has been reached in this ongoing study, an analysis of specific items or indexes within the RPQ, PCL, and CES-D will be performed. For example, the PCS measure employed (RPQ) has been shown to differentiate between minor trauma patients with and without mild TBI,[29] but some items are more specific for TBI than others. It is also conceivable that some of these individuals reporting AOC experienced a stress-induced disassociation rather than a TBI that might be internalized as a gap or noncontinuous memory.

In our analysis, using a combined index of all 3 studied AOC items, there were significant relations with severity of current PCS, PTSD, depression, and pain symptoms. This index may be a model of mild TBI diagnostic certainty in which having all 3 AOC items negative indicates "no TBI," having only 1 positive item indicates "possible TBI," and having 2 or 3 positive items indicates "definite TBI." As such, it suggests that an

TABLE 3 *Comparisons of current symptom measures among AOC items*[a]

	RPQ Mean (SD)	SF-MPQ Mean (SD)	PCL-C Mean (SD)	CES-D Mean (SD)
Memory Gap				
No	26.10 (14.08)	10.17 (7.70)	45.00 (15.88)	18.95 (8.10)
Yes	33.14 (17.24)	17.20 (6.19)	57.33 (13.76)	26.43 (8.56)
Difference	− 7.04 (14.62)	− 7.03 (7.47)	− 12.35 (15.55)	− 7.47 (8.18)
t (DF)	− 1.64 (82)	− 3.31 (83)	− 2.80 (84)	− 3.11 (78)
P	.1038	.0014	.0064	.0026
Continuous Memory				
Yes	26.18 (14.58)	10.27 (7.60)	45.31 (15.87)	19.24 (8.40)
No	34.55 (14.60)	18.33 (6.10)	58.42 (13.59)	26.08 (7.74)
Difference	− 8.37 (14.59)	− 8.06 (7.42)	− 13.11 (15.59)	− 6.85 (8.31)
t (DF)	− 1.77 (82)	− 3.49 (83)	− 2.70 (84)	− 2.63 (78)
P	.0798	.0008	.0083	.0102
LOC Observed				
No	25.15 (14.60)	10.37 (7.60)	45.88 (15.61)	19.59 (7.65)
Yes	35.06 (12.99)	15.59 (7.89)	51.89 (17.72)	22.76 (11.44)
Difference	− 9.90 (14.28)	− 5.22 (7.66)	− 6.01 (16.06)	− 3.18 (8.57)
t (DF)	− 2.61 (82)	− 2.51 (83)	− 1.41 (84)	− 1.36 (78)
P	.0108	.0139	.1620	.1787

Abbreviations: CES-D, Centers for Epidemiological Studies Depression Scale; DF, degrees of freedom; LOC, loss of consciousness; PCL-C, PTSD (posttraumatic stress disorder) Checklist, Civilian Version; RPQ, Rivermead Postconcussion Symptom Questionnaire; SD, standard deviation; SF-MPQ, Short Form McGill Pain Questionnaire.
[a]Max sample size is 87 subjects, but varies due to missing data. The total sample size for each analysis is equal to the DF + 2.

earlier blast-induced mild TBI plays a role in the development of not only PCS, but also depression, chronic pain, and PTSD, at least as determined by screening tools such as the PCL and CES-D. Therefore, attempts such as that of Hoge et al[28] to disentangle mild TBI sequelae (PCS) from traumatic stress sequelae (PTSD) in this population by controlling for current PTSD symptoms may lack validity. It also suggests that mild TBI is a significant precursor of chronic neuropsychiatric symptoms after military blast exposure rather than a transient

TABLE 4 *Comparisons of current symptom measures by number of positive AOC items (out of 3)*

	Positive AOC Items	Mean	SE	95% CI	*F* (DF1, DF2)	*P*
RPQ	2 or 3	34.56[a]	4.77	(25.06, 44.05)	3.67 (2, 81)	.0267
	1	32.58[a]	3.29	(26.04, 39.12)		
	None	24.30[b]	1.91	(20.50, 28.11)		
SF-MPQ	2 or 3	18.40[a]	2.29	(13.84, 22.96)	8.93 (2, 82)	.0003
	1	14.50[a]	1.71	(11.10, 17.90)		
	none	9.21[b]	0.96	(7.30, 11.12)		
PCL	2 or 3	58.70[a]	4.93	(48.89, 68.51)	4.08 (2, 83)	.0204
	1	49.95[a,b]	3.58	(42.83, 57.07)		
	None	44.18[b]	2.07	(40.07, 48.29)		
CES-D	2 or 3	27.40[a]	2.61	(22.21, 32.59)	4.64 (2, 77)	.0125
	1	20.71[b]	2.00	(16.73, 24.69)		
	None	18.77[b]	1.13	(16.52, 21.03)		

Abbreviations: CES-D, Centers for Epidemiological Studies Depression Scale; CI = confidence interval; DF1 = numerator degrees of freedom; DF2 = denominator degrees of freedom; PCL, PTSD (posttraumatic stress disorder) Checklist; RPQ, Rivermead Postconcussion Symptom Questionnaire; SE = standard error; SF-MPQ, Short Form McGill Pain Questionnaire.
Pairwise means that show significant difference are denoted by differing lettered superscript (ie, RPQ mean value[a] is significantly different from RPQ mean value[b]).

self-limiting injury. This contrasts with studies of mild TBI secondary to motor vehicle collision, in which the diagnosis of mild TBI has not been shown to relate to chronic symptoms.[30,31]

Given the DoD and VA goals of high sensitivity in mild TBI screening assessments, this study's findings suggest that these screens would benefit from multiple items probing for AOC. Additional diagnostic steps are also probably needed on positive screens to enhance diagnostic specificity. Interviews, which would permit further vetting of contradictory questionnaire responses, have been claimed by some to be more valid than questionnaires as a diagnostic tool for mild TBI.[32] However, the diagnostic accuracy of an unstructured interview is limited by the degree of examiner thoroughness, experience, expertise, and bias in formatting questions and interpretation of responses. Powell and colleagues,[12] Schwab and colleagues,[15] and Diamond and colleagues[16] each described loose elements of a semistructured interview for diagnosing mild TBI, all of which may have similar limitations.

Formal structured interviews that rely almost exclusively on history have been developed, validated, and utilized extensively in other conditions, so it is reasonable to conclude that they should be applicable to the mild TBI population as well. They are considered the criterion standard for diagnostic accuracy in most mental health conditions, against which shorter self-administered questionnaires are typically assessed psychometrically.[33–35] While standardized mental status examinations have been introduced for the diagnosis of acute mild TBI,[11] they are not applicable for the retrospective, postacute diagnosis. The OSU TBI-ID represents the only structured interview for the postacute diagnosis of an earlier mild TBI. As noted earlier, the OSU TBI-ID has shown high reliability only when LOC is reported and its predictive validity is weak, so its specificity and sensitivity for mild TBI are unknown.

Development of a valid structured interview for the postacute diagnosis of an earlier mild TBI will likely aid the parsing of the etiology of lingering, nonspecific symptoms in those who have sustained an earlier trauma, such as blast. We have developed an alternative fully structured mild TBI interview that will be employed with subsequent participants of this ongoing study of military blast exposure.

The primary limitation of this and similar postdeployment setting studies is the potential bias in the subjects' self-report of their past experience and early symptoms. Although patient self-report is the customary method for diagnosing mild TBI, the lag time from injury to our evaluation may have introduced recall bias. Also, although this research was separate from clinical and compensation processes, secondary gain bias cannot be excluded. We plan future studies that will include interview vetting of contradictory or illogical responses and assessing for feigned or "nonorganic" effort on impairment testing that might indicate symptom magnification. Another limitation, as noted earlier in the discussion, is that the PCL-C and CES-D were developed as screening instruments for PTSD and depression respectively, and consequently they have limited diagnostic specificity. Lastly, insufficient sample size may have prevented achieving statistical significance in the several ANOVA tests that appeared to have meaningful nominal differences.

CONCLUSIONS

Mild TBI is a difficult diagnosis to make postacutely, because by definition any early objective findings generally resolve rapidly. In the absence of valid, first responder documentation or witness corroboration, the late diagnosis of mild TBI is based entirely on self-report that centers on identifying an initial period of AOC associated with a plausible injury mechanism. In this questionnaire-based study, some inconsistencies were found in subjects' responses to AOC items, suggesting that a structured interview may improve specificity for making the diagnosis of mild TBI historically. Nonetheless, the questionnaire items probing for AOC that were analyzed in this study are each associated with current symptom distress. This implies that mild TBI has a role in the development of chronic neuropsychiatric symptoms after blast exposure.

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Factor Analysis of Persistent Postconcussive Symptoms Within a Military Sample With Blast Exposure

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Objective: To determine the factor structure of persistent postconcussive syndrome symptoms in a blast-exposed military sample and validate factors against objective and symptom measures. **Setting:** Veterans Affairs medical center and military bases. **Participants:** One hundred eighty-one service members and veterans with at least 1 significant exposure to blast during deployment within the 2 years prior to study enrollment. **Design:** Confirmatory and exploratory factor analyses of the Rivermead Postconcussion Questionnaire. **Main Measures:** Rivermead Postconcussion Questionnaire, PTSD (posttraumatic stress disorder) Symptom Checklist–Civilian, Center for Epidemiological Studies Depression scale, Sensory Organization Test, Paced Auditory Serial Addition Test, California Verbal Learning Test, and Delis-Kaplan Executive Function System subtests. **Results:** The 3-factor structure of persistent postconcussive syndrome was not confirmed. A 4-factor structure was extracted, and factors were interpreted as reflecting emotional, cognitive, visual, and vestibular functions. All factors were associated with scores on psychological symptom inventories; visual and vestibular factors were also associated with balance performance. There was no significant association between the cognitive factor and neuropsychological performance or between a history of mild traumatic brain injury and factor scores. **Conclusion:** Persistent postconcussive symptoms observed months after blast exposure seem to be related to 4 distinct forms of distress, but not to mild traumatic brain injury per se, with vestibular and visual factors possibly related to injury of sensory organs by blast. **Key words:** *blast*, *factor analysis*, *postconcussive syndrome*, *Rivermead Postconcussion Questionnaire*, *traumatic brain injury*

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The authors declare no conflicts of interest.

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"PERSISTENT POSTCONCUSSION SYNDROME" (PPCS) is a condition of nonresolving neurologic and behavioral symptoms following a concussion or mild traumatic brain injury (mTBI). It is recognized in the current editions of both the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*), and the *International Classification of Diseases, Tenth Revision* (*ICD-10*). At a minimum, diagnosis requires a prior traumatic brain injury (TBI) and persistence of at least 3 "postconcussive symptoms." Symptoms differ somewhat across diagnostic manuals but generally include headaches, dizziness, fatigue, irritability, sleep disturbance, depression/anxiety, sensory, and cognitive symptoms (*ICD-10*). While these symptoms are commonly reported after a concussion, it is their long-lasting nature that is considered the pathology of "PPCS." Three months postinjury is the generally accepted outer time frame for recovery, beyond which chronic symptoms merit the term "PPCS."[1] In the absence of objective markers of the condition, clinicians rely on patients' report of their symptoms to detect PPCS, often using symptom inventories such as the Rivermead Postconcussion Questionnaire (RPQ),[2] a measure recommended by the National Institute of Neurological Disease and Stroke.

It is important to note that the origins of PPCS are unresolved.[3,4] The symptoms may be directly related to the mTBI and/or may be consequences of maladjustment, depression, or unmet expectations; furthermore, many PPCS symptoms are common in the general population. In addition, it is very difficult to distinguish PPCS symptoms from some other possible sequelae of a head injury (such as depression). For example, 5 of the 9 current criteria for major depressive disorder are present on the 16-item RPQ. PPCS symptoms also exhibit unclear diagnostic significance for the incident mTBI(s): the overall number of PPCS symptoms endorsed did not discriminate between mTBI groups at 3 months postinjury.[5] Therefore, it is difficult to interpret both overall scores on the inventory and individual questions taken alone.

Because of symptom overlap, it is useful to examine higher-order structure, that is, how symptoms group together. Factor analysis is well suited to the question of interrelation among a diverse set of symptoms. Factors reflect distinct latent variables underlying the covariance among symptoms and so redefine a collection of symptoms as a smaller group of clusters. Because factors are more reliable measures than individual symptoms, they may be useful in predicting recovery, measuring the effects of risk factors, and may better differentiate PPCS and mTBI late effects from other similar disorders. Previous studies have found that, in comparison with other injuries, a history of mTBI seems to differentially increase the somatosensory and cognitive types of symptoms. When comparing mTBI with orthopedic controls, those with a history of mTBI endorse more somatic and cognitive symptom groups, with dizziness consistently endorsed at a higher rate in mTBI across studies.[6,7] Dizziness, visual symptoms, and cognitive symptoms were higher in cases of mTBI than in persons with chronic pain.[8] In contrast, distress most strongly affects the reporting of emotional and cognitive symptoms: patients with TBI and psychiatric comorbidities endorsed more symptoms overall than those with TBI alone, but specifically more cognitive and affective symptoms.[9]

The RPQ has been subjected to factor analyses in previous studies using civilian samples. In a study of mild to moderate TBI, Potter et al[10] found that a confirmatory factor analysis (CFA) with a single factor did not fit the RPQ data well, but 3- and 2-factor models demonstrated better and equally good fit. For the 2-factor model, the cognitive symptoms seemed to form a distinct factor while the remaining (emotional and somatic) loaded together. An exploratory factor analysis (EFA) in civilians[11] described 2- and 3-factor structures identical to those of Potter et al, supporting the validity of these 2 models; the 3-factor structure in particular being widely accepted. Collectively, these findings indicate that more than one process is implicated in the generation of PPCS symptoms (eg, not just general distress) and that there may be important clusters of symptoms within the postconcussive syndrome.

Nevertheless, PPCS symptoms can be moderated by other comorbid conditions such that symptom structures may not generalize across mTBI groups. Herrmann et al[12] performed an EFA on 96 individuals with mild to moderate TBI who exhibited symptoms of major depressive disorder on a structured interview. Again, the results supported that multiple latent variables underlie the RPQ score. Three factors were extracted and were described as a combined emotional/cognitive factor, a somatic factor, and a visual factor. As these differed in structure compared with the factors derived from the unspecified samples of Potter et al[10] and Lannsjö et al,[11] these data support the notion that major depression after TBI affects the experience of postconcussive symptoms.

PPCS SYMPTOMS IN THE MILITARY BLAST-EXPOSED POPULATION

Many individuals deployed during recent US military conflicts have experienced a blast, most often from improvised explosive devices. Blasts are reported to cause acute alterations in consciousness, whether by the primary blast wave or by striking or being struck by an object,[13–15] and blasts are considered a risk factor for mTBI. Blast-exposed individuals are a sizeable population presenting for evaluation and treatment in military and Veterans Health Administration (VHA) medical facilities and are also subject to mandatory TBI evaluations in the VHA system. PPCS symptoms after military-related blast generally seem similar in severity to those of other military groups,[16–18] but certain individual symptoms (headaches, tinnitus, hearing loss) were shown to be more likely to occur in blast-injured than in non–blast-injured populations.[13,16,18] In addition, the circumstances under which military blast-exposed individuals experienced an mTBI are intensely stressful, as are the circumstances that may accompany their recovery (other injuries, sometimes severe, long separations from family, career changes if leaving the military, to name a few). Consequently, deployed service members and veterans with blast exposure and/or mTBI are also at a high risk for depression and posttraumatic stress disorder (PTSD).[19] Thus, there are many reasons to expect that PPCS symptom patterns in this population may differ from those that comprise the standard model.

Although TBI is not a universal consequence of blast exposure, both blast-exposed individuals who did and did not sustain mTBI routinely present to VHA and other clinicians with PPCS-like symptoms. The RPQ is commonly used within this population to track outcomes, to direct treatment for mTBI, to estimate symptom burdens for administrative purposes, and to

test relations with risk factors and biomarkers in research. However, its factor structure in this population is not known, limiting the utility of the RPQ in all of these applications. The primary aim of this study was to describe the symptom structure of the RPQ in a blast-exposed military sample at a high risk for mTBI. Furthermore, we aim to validate the factors using objective measures of functioning and psychiatric symptom measures.

METHODS

This study received all appropriate institutional review board and governmental approvals, and all subjects provided informed consent before data collection.

Participants

A total of 181 participants were included in this analysis. This study sample was derived from the first 196 participants who completed baseline assessments in a larger epidemiological study examining the effects of blast exposure.[20] All participants were active-duty service members or veterans, had been deployed to Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF), and had exposure to at least 1 blast event within the 2 years prior to enrollment. A *blast event* was defined as any of the following occurring during or shortly after the blast or explosion: feeling dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, or evacuated. The lone exclusion criterion was failure on neuropsychological effort testing as determined by the Test of Memory Malingering (TOMM).[21] Accordingly, 15 persons were excluded to yield the final sample size of 181. All participants were ambulatory and free of injury that would prevent them from engaging in regular physical activities.

The demographic and military characteristics of the sample are summarized in Table 1. The sample was primarily male (96%), with an average age of 27.6 (SD = 7.9) years. The median number of months since most recent blast exposure was 9 (interquartile range = 6-15). The majority reported multiple blast exposures, with 36% reporting more than 5. Seventy-nine participants also underwent a diagnostic interview for TBI developed by one of the study investigators. The interview was administered by a trained research assistant and consisted of both structured and unstructured components. The structured component focused on the acute effects of injury experienced by the patient (amnesia, loss or alteration of consciousness). Responses were independently reviewed by a group of 5 experienced TBI physicians who individually rated each participant's worst (or only) blast exposure as "yes" versus "no" in reference to the Department of Defense/Department of Veterans Affairs common definition for mTBI.[22] A consensus diagnosis was obtained for each participant on the basis of a simple majority. Of these 79 participants, 66 (84%) received a diagnosis of mTBI and 13 (16%) did not (had no TBI).

TABLE 1 *Sample characteristics*

Characteristic	Count	%
Sex		
Female	7	3.9
Male	174	96.1
Marital status		
Married	85	47.0
Divorced	15	8.3
Single	81	44.8
Race		
Caucasian	143	79.0
African American	27	14.9
Other	11	6.1
Ethnicity		
Hispanic	15	8.3
Non-Hispanic	166	91.7
Level of education		
Less than high school	2	1.1
High school graduate	94	51.9
Some college	62	34.3
College graduate	20	11.0
Postgraduate degree	3	1.7
No. blasts		
1	36	20.0
2	36	20.0
3	25	13.9
4	14	7.8
5	5	2.8
>5	64	35.6
Branch of service		
Air Force	2	1.1
Army	78	43.1
Navy	4	2.2
Marine Corps	97	53.6
Army and Marine Corps	2	1.1
PTSD (PCL total score ≥50)		
No	105	58.3
Yes	75	41.7
Severe or probable major depression (total CES-D score ≥27)		
No	143	81.7
Yes	32	18.3

Abbreviations: CES-D, Center for Epidemiological Studies Depression; PCL, civilian version of the PTSD Checklist; PTSD, posttraumatic stress disorder.

Procedure

All measures were completed by each participant individually in a private testing space, with a research coordinator or assistant available for questions.

Symptom measures

Postconcussive symptoms

The RPQ consists of 16 items: headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed/tearful, feeling frustrated/impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. The extent of each PPCS symptom is rated on a 5-point Likert scale, with 0 representing "not experienced at all" and 4 indicative of "a severe problem" as compared with before the blast experience. An individual was considered positive for PPCS if he or she rated 3 or more symptoms on the RPQ as 2 (greater than preinjury) or higher, in accordance with symptom criteria for postconcussional disorder from the *DSM-IV*.

Depressive symptoms

Participants completed the Center for Epidemiological Studies Depression (CES-D) scale.[23] The CES-D consists of 20 items designed to measure current symptoms of clinical depression. Participants rate from 1 to 3 the degree to which they have experienced that symptom in the past week. Possible total scores range from 0 to 60, with higher scores indicative of greater levels of depression.

Posttraumatic stress symptoms

Participants completed the civilian version of the PTSD Checklist (PCL).[24] The PCL consists of 17 questions assessing the *DSM-IV* criteria symptoms of PTSD. The degree to which the participant has been bothered by each PTSD symptom over the last month is rated on a 5-point Likert scale, with 1 representing "not at all" and 5 representing "extremely." The maximum total score is 80. The civilian version was used in lieu of the military version to avoid assuming that the most stressful life event was related to military service; the two versions are otherwise identical.

Neuropsychological testing

One hundred forty-one participants underwent neuropsychological testing across many domains as part of the larger study. Scores on tests of functions commonly affected by mTBI were selected a priori as outcome measures to be used in this study. These tests included the Long Delay Free Recall score of the California Verbal Learning Test, Second Version (CVLT-II; assesses short- and long-term verbal memory[25]), the 2.0-second pacing score of the Paced Auditory Serial Addition Test (PASAT; assesses selective attention and concentration[26]), and the Delis-Kaplan Executive Function System (DKEFS) Category Fluency and Category Switching subtests (DKEFS; assesses several executive and strategic processes[27]). Sixteen participants were missing PASAT scores due to a computer malfunction.

Balance testing

Data from computerized posturography testing using the Sensory Organization Test (SOT; NeuroCom, Clackamas, Oregon) were available for 139 participants. This test measures the degree of body sway in response to a shifting plate on which the subject is standing. Sensory information is systematically adjusted to be either an effective or ineffective cue for balance. A composite measure capturing general balance performance is provided by the SOT and was used as the outcome measure in this study. More details on computerized posturography testing have been described elsewhere.[28]

Statistical methods

The demographic, military, psychological (CES-D and PCL), and postconcussive (RPQ) characteristics of the study sample were described using frequency counts with percentages for categorical variables and means/medians with standard deviations/interquartile ranges for continuous variables.

Confirmatory factor analysis

A CFA of the 3-factor structure from a published study within a civilian population[10] was conducted. The CFA was performed on the covariance matrix and was fit using the CALIS procedure in SAS v.9.3 (SAS Institute Inc, Cary, North Carolina). Global goodness of fit of the CFA model was evaluated using the standardized root mean square (SRMR), the root mean square error of approximation (RMSEA), the comparative fit index (CFI), and the nonnormed fit index (NNFI). The model was considered to have an adequate fit if SRMR was less than 0.06,[29] RMSEA was less than 0.08,[30] and both CFI and NNFI exceeded 0.9.[31,32]

Individual item reliabilities were examined, and the composite reliability index was calculated to assess the internal consistency of the indicators measuring a given factor. A value of 0.70 was considered the minimally acceptable level of reliability for each construct. In addition, variance-extracted estimates were calculated to describe the percentage of variance captured by each factor.

Exploratory factor analysis

An EFA was planned in the event that the CFA was not successful. The number of factors explored was determined by a scree plot, principal components analysis, parallel analysis, and a priori research using another PPCS inventory (the Neurobehavioral Symptom Inventory) in a similar population. The EFA was conducted

on the correlation matrix using the FACTOR procedure in SAS v.9.3. The factors were expected to be correlated and thus an oblique (promax) rotation was used. Squared multiple correlations were used as prior communality estimates, and the maximum likelihood extraction method was used. An item was assumed to load on a given factor if the factor loading was at least 0.40 for that factor and less than 0.40 for all other factors.

Additional analyses

To characterize the sample with regard to the extracted factors, we calculated the factor scores for each participant using the regression method.[33] Bivariate correlations and analyses of variance were used to assess the relations among factor scores, symptom and performance measures, and TBI status. Analysis of variance was conducted on regression residuals where it was desired to control for the effects of a continuous variable on the dependent variable. It should be noted that the number of subjects available for each analysis varied and so the sample size varied for each of the estimated correlations.

RESULTS

Participants

Psychological characteristics

Mean CES-D score was 17 (SD = 2), which falls between "possible" and "probable" depressive disorder.[34] Mean PCL score was 47.1 (SD = 15), nearing the cutoff score of 50 for PTSD diagnosis,[24] a cutoff point accepted for use in military samples.[35] Thus, this sample is characterized by moderately elevated depressive symptoms and a very high degree of PTSD symptoms. Neither PCL nor CES-D scores were significantly different between TBI-positive versus TBI-negative groups in the subsample for whom TBI status was determined.

RPQ postconcussive symptoms

RPQ scores were normally distributed with a mean total score of 28 (SD = 13). One hundred sixty four participants (90.6%) met symptom criteria for PPCS. Compared with previously described mTBI samples, the mean score is consistent with a PPCS severity in the moderate range, more than 90% of a nonclinical sample,[10] and thus the sample was highly symptomatic. TBI status (of those for whom it was determined) was not significantly related to RPQ score ($F_{1,77} = 0.139$, $P > .05$), nor was the number of blast exposures ($F_{6,174} = 0.891$, $P > .05$). The correlation matrix for the 16 RPQ items is shown in Table 2. There was moderate correlation among most of the items (range $r = 0.11$-0.75) and thus the data were suited for data reduction.

Neuropsychological performance

Test scores were normally distributed with standardized means near the general population mean (DKEFS Category Fluency mean $z = -0.2$; Category Switching mean $z = 0.4$, and CVLT-II Delayed Free Recall mean $z = -0.55$), with the exception of the PASAT with a mean score of $z = -1.02$. TOMM score distribution was heavily weighted to the ceiling, with 88% having the highest possible score and 1% just above the cutoff score for invalid effort.

Confirmatory factor analysis

The factor loadings from the CFA are shown in Table 3. The composite reliability indices were all over 0.7 (see Table 3), indicating that each factor had good internal consistency. The variance-extracted estimates for the emotional and cognitive factors exceeded the minimally acceptable level of 0.50, indicating that these factors demonstrate good validity. However, the variance-extracted estimate for the somatic factor was less than 0.50 (ie, the somatic factor explained only 34.4% of the variance) and thus the validity of this construct is questionable. Finally, the model fit statistics were all unsatisfactory (SRMR = 0.0798 > 0.06; RMSEA = 0.1034 > 0.08; CFI = 0.8660 < 0.9; and NNFI = 0.8408 < 0.9), suggesting that the proposed 3-factor model did not adequately fit the data. In summary, the results of the CFA indicated that the 3-factor solution did not conform well in the present sample.

Exploratory factor analysis

Because the confirmatory analysis was unsuccessful, we next performed EFA. The scree plot indicated that 4 factors would likely improve on the 3-factor model but that 5 or more would not add substantial explanatory power. Principal components analysis showed that 3 factors had eigenvalues greater than 1, and parallel analysis indicated that 2 factors generated larger eigenvalues than a random data set. The 4-factor solution was preferred, because this solution showed the fewest items without strong loading and the fewest cross-loadings. This solution was also preferred from a theoretical standpoint because the 2 sensory systems, visual and vestibular, were clearly separated, which may prove useful in predicting specific clinical outcomes. The factor loadings for the 4-factor solution are shown in Table 4. The interfactor correlations for the 4-factor solution are shown in Table 5. A high degree of correlation among the 4 factors was observed. Factor 1 (noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed or tearful, feeling frustrated or impatient, and restlessness) can be described as an emotional factor, factor 2 (forgetfulness, poor concentration, and taking longer to think) can be

TABLE 2 *Correlation matrix for the 16 symptoms measured by the Rivermead Postconcussion Questionnaire*

	Headaches	Dizziness	Nausea/ vomiting	Noise sensitivity	Sleep disturbance	Fatigue	Irritability	Depressed	Frustrated	Forget fulness	Poor concentration	Longer to think	Blurred vision	Light sensitivity	Double vision	Restlessness
Headaches	1.00	0.46	0.28	0.36	0.44	0.38	0.38	0.31	0.39	0.47	0.34	0.43	0.40	0.44	0.26	0.36
Dizziness		1.00	0.45	0.28	0.30	0.43	0.26	0.32	0.30	0.42	0.32	0.34	0.41	0.32	0.33	0.37
Nausea/vomiting			1.00	0.31	0.26	0.36	0.19	0.33	0.24	0.15	0.11	0.09	0.35	0.35	0.29	0.32
Noise sensitivity				1.00	0.52	0.41	0.50	0.37	0.53	0.45	0.45	0.49	0.31	0.34	0.23	0.45
Sleep disturbance					1.00	0.52	0.57	0.45	0.61	0.43	0.46	0.44	0.28	0.33	0.26	0.64
Fatigue						1.00	0.52	0.51	0.62	0.50	0.47	0.51	0.28	0.25	0.13	0.51
Irritability							1.00	0.50	0.75	0.44	0.45	0.52	0.22	0.20	0.23	0.53
Depressed								1.00	0.62	0.39	0.45	0.45	0.36	0.27	0.23	0.54
Frustrated									1.00	0.58	0.58	0.62	0.31	0.30	0.20	0.59
Forgetfulness										1.00	0.75	0.75	0.29	0.33	0.16	0.47
Poor concentration											1.00	0.73	0.25	0.26	0.17	0.41
Longer to think												1.00	0.32	0.31	0.24	0.49
Blurred vision													1.00	0.55	0.56	0.39
Light sensitivity														1.00	0.35	0.34
Double vision															1.00	0.29
Restlessness																1.00

TABLE 3 *Properties of the measurement model (confirmatory factor analysis)*

		Standardized loading	*t*	Indicator reliability	Error variance	Variance extracted
Somatic				0.822		0.344
Q1	Headaches	0.62	8.78	0.388	0.612	
Q2	Dizziness	0.57	7.82	0.321	0.679	
Q3	Nausea	0.47	6.21	0.216	0.784	
Q4	Noise sensitivity	0.65	9.27	0.423	0.577	
Q5	Sleep disturbance	0.71	10.49	0.510	0.490	
Q6	Fatigue	0.69	10.07	0.480	0.520	
Q13	Blurred vision	0.55	7.55	0.303	0.697	
Q14	Light sensitivity	0.54	7.29	0.286	0.714	
Q15	Double vision	0.42	5.48	0.173	0.827	
Emotional				0.857		0.602
Q7	Irritability	0.79	12.29	0.624	0.376	
Q8	Depressed	0.69	10.23	0.480	0.520	
Q9	Frustrated	0.90	14.88	0.802	0.198	
Q16	Restless	0.71	10.54	0.502	0.498	
Cognitive				0.896		0.741
Q10	Forgetfulness	0.87	14.25	0.758	0.242	
Q11	Poor concentration	0.85	13.68	0.718	0.282	
Q12	Taking longer to think	0.87	14.10	0.747	0.253	

TABLE 4 *Standardized factor loadings for 4-factor solution structure*

Item	Emotional	Cognitive	Visual	Vestibular
Noise sensitivity	**0.43**[a]	0.17	0.10	0.05
Sleep disturbance	**0.64**[a]	0.03	0.03	0.10
Fatigue	**0.48**[a]	0.17	−0.17	0.35
Irritability	**0.89**[a]	−0.01	−0.03	−0.11
Depressed	**0.58**[a]	0.02	0.09	0.10
Frustrated	**0.85**[a]	0.13	−0.02	−0.08
Restlessness	**0.55**[a]	0.05	0.13	0.14
Forgetfulness	−0.01	**0.90**[a]	−0.06	0.09
Poor concentration	0.14	**0.78**[a]	−0.02	−0.07
Taking longer to think	0.20	**0.73**[a]	0.10	−0.14
Blurred vision	−0.01	0.01	**0.83**[a]	0.03
Light sensitivity	−0.01	0.11	**0.51**[a]	0.14
Double vision	0.06	−0.08	**0.67**[a]	−0.03
Dizziness	−0.09	0.23	0.10	**0.59**[a]
Nausea	0.14	−0.23	0.08	**0.66**[a]
Headaches	0.10	0.26	0.19	0.26

[a]Item assumed to load on a given factor if the factor loading was greater than 0.4 for that factor and less than 0.4 for all other factors.

TABLE 5 *Interfactor correlations (4-factor solution structure)*

	Emotional	Cognitive	Visual	Vestibular
Emotional	1.00	0.62	0.41	0.46
Cognitive		1.00	0.37	0.38
Visual			1.00	0.55

considered a cognitive factor, factor 3 (blurred vision, light sensitivity, and double vision) can be described as a visual factor, and factor 4 (dizziness and nausea) appears to be a vestibular-type factor. Headaches did not load on any of the 4 factors. The final factor (vestibular) is identified by only 2 items and therefore may be empirically weak compared with the first 2 factors. Internal consistency measures (Cronbach α) of factors were acceptable to very high: emotional factor (0.89), cognitive factor (0.90), visual factor (0.71), and vestibular factor (0.62). The lower α value of the vestibular factor can be attributed in part to the small number of items comprising this subscale.

Factor scores and subscale validity

Factor scores, in general, were normally distributed, with some positive skewness in the visual factor 3 (skewness = 1.0). Results of criterion validity analysis of factor scores are shown in Table 6. We adjusted for multiple comparisons by decreasing the overall criterion for significance to .01. All factor scores were significantly correlated with the PCL and CES-D symptom measures. For the PCL and the CES-D scales, the proportion of total variance explained by each factor progressively declined from emotional to cognitive, visual, and vestibular factors. The CES-D scale showed weaker relations with all factors than did the PCL. The objective measure of balance performance (the SOT composite score) was significantly related to only the vestibular and visual factor scores. No neuropsychological test score was significantly related to any factor score, with the exception of the DKEFS Category Fluency score, which was significantly associated with the vestibular factor score. No factor scores were significantly related to TBI status even after removing the effect of PCL score.

DISCUSSION

We found that the standard 3-factor solution for PPCS measured by the RPQ was not optimal in this blast-exposed military population. Instead, symptoms were better described by a 4-factor solution with emotional, cognitive, visual, and vestibular factors. All factors were related to measures of psychological status; sensory factors were related to balance performance; finally, no factors were related to TBI status. As with previous factor analytic studies of PPCS inventories, our findings do not support a unified construct of PPCS symptoms. Instead, there are multiple processes contributing to PPCS, producing coherent and distinct clusters of symptoms. This extractability of factors implies that individuals experiencing PPCS after blast exposure should not be presumed to lie on a unitary "PPCS" spectrum, but rather 4 spectra in more specific domains, and that differing pathoetiologies may exist. As with other complex, multidimensional constructs such as personality and pain, "PPCS" may be a general term that requires refinement to be fully and accurately described.

PPCS symptom structure in the military blast population

PPCS symptom structure in the present population differed from that previously described in 2 civilian samples recruited from emergency departments in Sweden and the United Kingdom.[10,11] This finding supports the notion that the perception or experience of postconcussive symptoms is different in the present population. Previous factor analytic studies of PPCS in the recently deployed blast-exposed population have also found more complex factor solutions than the standard 3-factor model,[36,37] whereas, in contrast, pre-OEF/OIF samples, neither combat- nor blast-exposed, have demonstrated good fit with the standard.[38] There are many distinguishing features of the present sample that may contribute to this difference, among which are psychiatric comorbidities, combat experience, multiple potential brain injuries (due to a high level of blast exposure), particular expectations or knowledge of their injuries, and/or the blast(s) itself.

Blast injury has been a common historical characteristic across the samples where complex PPCS factor structures have been found, but these studies suffer from the same potential confounding variables that usually accompany military blast injury. In particular, combat exposure and its psychological consequences are likely to have a strong influence on processes underlying symptom reporting. PTSD symptoms were very prominent in this sample, and depressive symptoms were moderately elevated on average. Depression has been shown to be a strong factor in PPCS symptom reporting after mTBI in this same population[39] as have posttraumatic stress symptoms,[16,40] with the conclusion being that it is hazardous to attribute PPCS symptoms to mTBI in the presence of these comorbidities. Taken together, though, this and other factor analytic studies confirm that contributing processes to PPCS symptoms in this population are likely more complex than the standard model, with the same symptoms possibly having different origin, meaning, or recovery course than in non–blast-exposed and/or nonmilitary groups.

Interpretation of the factors

The first factor, the emotional factor, was characterized by more items than the similar factor in civilian samples, suggesting greater complexity in the present population. The emotional factor in particular overlapped considerably with posttraumatic symptoms, suggesting that the emotional factor structure may be attributable in part to PTSD. This interpretation is

TABLE 6 *Criterion validity of Rivermead Postconcussion Questionnaire factors*

	n	Factor	Slope	R^2	*t*	*P*
PCL total	180	Emotional	8.99	0.52	13.88	<.001[a]
		Cognitive	6.68	0.31	8.91	<.001[a]
		Visual	6.34	0.19	6.54	<.001[a]
		Vestibular	6.46	0.19	6.39	<.001[a]
CES-D total	175	Emotional	5.02	0.35	9.63	<.001[a]
		Cognitive	3.82	0.22	7.02	<.001[a]
		Visual	2.80	0.08	3.93	<.001[a]
		Vestibular	4.28	0.18	6.17	<.001[a]
SOT composite	139	Emotional	−1.60	0.04	−2.40	.018
		Cognitive	−1.30	0.03	−2.10	.037
		Visual	−2.39	0.08	−3.35	.001[a]
		Vestibular	−3.23	0.14	−4.67	<.001[a]
DKEFS	142	Emotional	−0.69	0.01	−1.15	.253
Category Fluency		Cognitive	−0.10	0.00	−0.18	.860
		Visual	−0.82	0.01	−1.19	.237
		Vestibular	−1.76	0.05	−2.61	.010[a]
DKEFS	142	Emotional	0.07	0.00	0.33	.745
Category Switching		Cognitive	−0.02	0.00	−0.10	.920
		Visual	0.03	0.00	−0.11	.913
		Vestibular	0.01	0.00	0.05	.961
PASAT	126	Emotional	0.41	0.00	0.41	.685
2.0-s pacing		Cognitive	−0.35	0.00	−0.39	.698
		Visual	−0.45	0.00	−0.39	.701
		Vestibular	−0.52	0.00	−0.45	.656
CVLT-II	142	Emotional	−0.12	0.00	−0.48	.629
Long Delay Cued Recall		Cognitive	−0.40	0.02	0.02	0.081
		Visual	−0.36	0.01	−1.28	.204
		Vestibular	−0.43	0.02	−1.53	.128
CVLT-II	142	Emotional	−0.33	0.01	−1.22	.223
Long Delay Free Recall		Cognitive	−0.47	0.03	0.03	0.058
		Visual	−0.55	0.02	−1.82	.070
		Vestibular	−0.73	0.04	−2.44	.016
BVMT-R	142	Emotional	−0.10	0.00	−0.53	.599
Delayed Recall		Cognitive	−0.28	0.02	−1.68	.096
		Visual	−0.28	0.01	−1.37	.173
		Vestibular	−0.29	0.01	−1.40	.164
BVMT-R	142	Emotional	−0.07	0.02	−1.52	.132
Recognition hits		Cognitive	−0.10	0.04	−2.30	.023
		Visual	−0.05	0.01	−0.88	.383
		Vestibular	−0.08	0.02	−1.50	.136

Abbreviations: BVMT-R, Brief Visuospatial Memory Test–Revised; CES-D, Center for Epidemiological Studies Depression; CVLT-II, California Verbal Learning Test, Second Version; DKEFS, Delis-Kaplan Executive Function System; PCL, civilian version of the PTSD Checklist; PASAT, Paced Auditory Serial Addition Test; PTSD, posttraumatic stress disorder; SOT, Sensory Organization Test.
[a]Correlation significant at $P < .01$.

supported by (1) the high degree of PTSD symptoms in the current sample, (2) the finding that the relation between PTSD symptoms and this factor was the strongest observed in the study, and (3) the fact that the items that switched loading relative to the comparison sample are all related to symptoms of PTSD: noise sensitivity (vigilance), sleep disturbance (nightmares), and fatigue (secondary to sleep disturbance and vigilance). Depressive symptoms were also strongly related to emotional factor scores, supporting that this factor originates partly in perceived mood disturbance as well.

A second, cognitive, factor was observed that was correlated with—but independent of—the emotional factor. The cognitive factor was not related to objective cognitive performance as reflected by the tests in this analysis. Thus, symptoms of cognitive dysfunction in this population may not be accompanied by actual impairment (and vice versa). In general, research has shown that individuals are often inaccurate in assessing their own cognitive abilities; instead, the strongest influence on self-assessment is self-esteem, not actual performance.[41] Therefore, a belief that one is impaired will have greater

influence on cognitive symptom reporting than the actual presence of impairment. The lack of a relation with TBI further supports the conclusion that high cognitive factor scores to some degree reflect a distressed self-perception with regard to cognition. This cognitive-focused distress may be generated in a number of ways: some individuals may respond to cognitive problems as a more "valid" expression of distress than emotional symptoms, or they may have expectations of poor cognition due to knowledge of mTBI. Symptoms may reflect their sense of increased mental effort required to maintain normal performance, which could stem from decreased cognitive reserves and/or accompanying PTSD or depression (symptoms of which were correlated with the cognitive factor). It is possible that the measures chosen for this study were not sensitive enough to capture participants' cognitive deficits, but since many studies using a variety of measures have shown that neuropsychological impairment resolves by 3 months after injury,[42] it is more likely that these participants are not cognitively impaired. It is also worth noting that many of the relations between the memory tests and the cognitive factor were marginally significant, showing the need for further study of this issue. However, as the present correlations were very small as well as nonsignificant, these results are not consistent with a strong relation between cognitive complaints and neuropsychological impairment.

Both somatic factors were significantly related to PCL and CES-D scores, suggesting that emotional distress was also implicated in these symptoms. At the same time, however, posttraumatic stress symptoms and depression explained less variance in the sensory factors than in the emotional and cognitive ones, suggesting that vestibular and visual symptoms were less a product of depression and anxiety than the other 2 types. Furthermore, both somatic factors were significantly related to balance behavior and the strongest relation with balance behavior was with the vestibular-type factor. This suggests a dysfunction of the balance network behind these symptoms. However, given that the balance dysfunction was presumed to result at least in part from TBI, it was unexpected that TBI status was not related to either the visual or vestibular factors. It is possible that one or multiple blasts could have caused a non-TBI injury (ie, no alteration of consciousness), such as inner ear, cervical, or eye damage, which would affect balance and elicit sensory symptoms. One executive function test was associated with the vestibular factor, suggesting that such injuries could affect this cognitive domain. More work is needed both to understand this relation and to investigate the potential dysfunctions of the visual, vestibular, and auditory systems that may contribute to the sensory symptoms measured by the RPQ.

While "somatic" symptoms are usually considered together when PPCS symptom structure is discussed (eg, Williams et al[43]; King[44]), there is support from the factor structure for separable sensory system dysfunction in the present population. There is a possibility that damage to the 2 systems (visual and vestibular) is not always symmetrical and thus the concept of "somatic" symptoms in this population may be misleading. It is possible that blast, cognitive dysfunction, distress symptoms, or responsiveness to interventions may relate differently to sensory deficits in different domains; these relations would not be detectable without considering the visual and vestibular symptoms separately. Furthermore, general "somatic" PPCS symptoms might be conceptually conflated with "somatization," a psychiatric process resulting in medically unexplained physical complaints.[45] In the present sample, some conventionally "somatic" complaints were better characterized as emotional (fatigue, noise sensitivity, and sleep disturbance), resulting perhaps in a less "somaticized" character for the visual and vestibular factors. However, at present, these factors are unsatisfactorily defined, due to small numbers of associated items and somewhat imprecise (dizziness) and selective (double vision but not reduced acuity or reading difficulty) symptoms. More questions might be added to the RPQ to adequately capture vestibular-type, visual, and auditory symptoms in order to increase the reliability and utility of these factors and enhance the instrument's sensitivity to distinct sensory system dysfunction, especially when used in a blast-exposed population.

Effect of mTBI on factor scores

We expected that the factor scores would differentiate between mTBI groups, particularly the cognitive and sensory factors, as these symptoms have shown some discriminative power in previous studies. However, in this study, TBI status was not related to the factor scores or the overall score on the RPQ, even after controlling for the effects of PTSD symptom severity. A reduction in power due to unequal group variances is not a likely explanation, because the differences in means in all cases were very small in relation to standard deviation and some means were actually higher for the non-TBI groups. This residual unexplained variance that was unrelated to mTBI suggests that nonspecific effects beyond PTSD (eg, of combat and deployment experience) strongly influence PPCS symptom reporting. Participants in this study were under a great deal of stress unrelated to trauma caused by pain, sleep deprivation, long periods of deployment, and separation from their families, among other factors. Both TBI-positive and TBI-negative groups had high levels of stress, PTSD symptoms, and depression symptoms. In this situation,

postconcussive symptom scores on the RPQ as written, even by factor, cannot discriminate the effects of the mTBI alone. Overall, the findings support that PPCS symptom reporting, even when considering factors independently, is strongly influenced by stressful injury circumstances, with mTBI having a negligible effect in this context.

Clinical significance

PPCS symptoms are often the basis for treatment and healthcare policy decisions, as well as conclusions regarding mTBI outcomes. Thus, it is essential to clarify as much as possible what PPCS symptoms reflect in the patient population being treated. Results of this study of a blast-injured military sample support previous findings that caution against considering PPCS symptoms as a unitary phenomenon or syndrome with a single cause and recovery course or as a collection of disparate symptoms. The 1995 statement of Cicerone and Kalmar is still relevant:

> We suggest that the depiction of patients as having a uniform postconcussive syndrome has frequently resulted in vague clinical characterizations, often with negative connotations. It may be more meaningful to think in terms of a number of possible postconcussive syndromes that have different symptom profiles and courses, despite some degree of overlap.[46(p.11)]

As research progresses, consideration should be given to the 4 separable domains with distinguishable contributing factors as described earlier.

Results do not support the use of the current RPQ factors as a stand-alone mTBI outcome measure in this postdeployment blast- and combat-exposed population. However, the factors presently described do appear to reflect meaningful and distinct features of subjective outcome from blast injury in a military setting. For instance, distinct cognitive and emotional types of distress were observed, which suggest that the nature of the postblast distress is neither general nor derived solely from emotional disturbance; thus, treatment solely for emotional disturbance may not be enough. Also, treatment and assessment for cognitive symptoms in this population should take into account the tenuous relation between complaints and neuropsychological dysfunction, as well as the distinct psychological issues that may generate cognitive symptoms (as opposed to emotional symptoms). Results support the current approach of VA Polytrauma Centers of treatment of "somatic" symptoms addressing specific sensory domains.[47] Clinicians examining interventions for PPCS may question whether a treatment is appropriate for PPCS in general or whether it may differentially affect symptom domains. Furthermore, the description of factors makes feasible the description of clinical subtypes of PPCS; such descriptions can generate new hypotheses about etiology and shape treatment approaches. Distinct treatment pathways may be needed for PPCS subtypes analogous to headache management where treatments differ for migraine versus tension-type headache.

Results also support that injury circumstances are relevant to the nature of PPCS, not only increasing or decreasing severity but also changing the interrelations of symptoms in complex ways. Biopsychosocial and individualized approaches that take this context into account, such as that advocated by Howe,[48] are in line with this finding. Future research will be needed to specify the role of blast injury and combat circumstances in generating symptoms and clarify how recovery from mTBI and the resolution of PPCS may differ for this population. At this time, caution is indicated in comparing either overall severity or individual symptoms between blast-exposed military samples and others with mTBI, as the same symptom may have different causes in groups with different injury circumstances.

Limitations

Some limitations are noted to this study. First, no RPQ data from a non–blast-injured military group were available to compare with this sample. Therefore, we are unable to draw conclusions regarding the specific effects of blast on PPCS symptom reporting. Second, the inclusion criteria for this study did not include a definitive diagnosis of mTBI, so the sample includes some participants with blast exposure who did not sustain an accompanying mTBI. However, the sample is representative of that encountered in military and veterans medical facilities, where many individuals are evaluated for PPCS symptoms when the history of mTBI is not definitive. As the sample was predominantly Caucasian, non-Hispanic, and male, the patterns of symptom complaint and their external validity may not generalize to females or other racial or ethnic groups. Symptom patterns may not generalize to other recovery periods whether earlier or later. Finally, potential participants who failed effort measures were removed from this sample, a procedure not commonly performed in factor analyses of PPCS symptoms. This may be considered a limitation when comparing the present results with other similar studies. However, additional analyses indicated that this action did not affect overall factor structure or significance, only loading and criterion validity correlation values.

Removal of those who failed effort measures may actually be viewed as a strength of this study, as confounding issues of symptom complaint and performance validity were minimized, particularly important for tests of associations between cognitive performance and PPCS symptoms. Furthermore, objective performance measures were used to examine the subscale factors for criterion validity. TBI status was determined by diagnostic

interview with each participant and so many problems associated with self-report of TBI have been avoided.

Future directions

This study builds on previous reports of PPCS symptoms in blast-exposed military populations, supporting a 4-factor structure in this group with distinct sensory domains of visual and vestibular symptoms. Future directions include better defining PPCS after blast and the potential clinical subtypes of the disorder, based on the present factors. Important questions remain concerning the role of multiple subconcussive blast injuries and brain function, blast-impaired sensory function, and comorbid mood and anxiety disorders in the development of symptoms in each domain. Future studies should examine the relations of each domain to other measures of cognition not presently tested, such as basic choice reaction time, and more in-depth evaluation of sensory function, such as static and dynamic visual acuity. Conversely, more data are needed concerning the relations between true sensory and cognitive impairment and symptom report. These questions of symptom predictive value, sensitivity, and comprehensiveness are critical to ensure that the most relevant PPCS outcomes are measured. External validation of PPCS symptoms–the sensory symptoms in particular–is an underdeveloped area of research. It is hoped that the field will continue to move toward better validated, sensitive, specific, and empirically defined PPCS symptoms for both blast-injured and non–blast-injured individuals.

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Longitudinal Interactions of Pain and Posttraumatic Stress Disorder Symptoms in U.S. Military Service Members Following Blast Exposure

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Abstract: Military personnel returning from conflicts in Iraq and Afghanistan often endorse pain and posttraumatic stress disorder (PTSD) symptoms, either separately or concurrently. Associations between pain and PTSD symptoms may be further complicated by blast exposure from explosive munitions. Although many studies have reported on the prevalence and disability associated with polytraumatic injuries following combat, less is known about symptom maintenance over time. Accordingly, this study examined longitudinal interactive models of co-occurring pain and PTSD symptoms in a sample of 209 military personnel (mean age = 27.4 years, standard deviation = 7.6) who experienced combat-related blast exposure. Autoregressive cross-lagged analysis examined longitudinal associations between self-reported pain and PTSD symptoms over a 1-year period. The best-fitting covariate model indicated that pain and PTSD were significantly associated with one another across all assessment periods, χ^2 (3) = 3.66, *P* = .30, Tucker-Lewis index = .98, comparative fit index = 1.00, root mean squared error of approximation = .03. PTSD symptoms had a particularly strong influence on subsequent pain symptoms. The relationship between pain and PTSD symptoms is related to older age, race, and traumatic brain injury characteristics. Results further the understanding of complex injuries among military personnel and highlight the need for comprehensive assessment and rehabilitation efforts addressing the interdependence of pain and co-occurring mental health conditions.

***Perspective:** This longitudinal study demonstrates that pain and PTSD symptoms strongly influence one another and interact across time. These findings have the potential to inform the integrative assessment and treatment of military personnel with polytrauma injuries and who are at risk for persistent deployment-related disorders.*

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***Key words:** Chronic pain, stress disorders, posttraumatic, military personnel, blast injuries, longitudinal studies.*

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Significant numbers of military personnel returning from Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) endorse pain and posttraumatic stress disorder (PTSD) symptoms, often concurrently. Estimates show that up to 20% of OEF/OIF/OND veterans meet criteria for PTSD,[14,32] and upwards of 81% of OEF/OIF/OND veterans report ongoing or new pain following their military service.[10,21] Further, these symptoms frequently co-occur, representing a common polytrauma cluster of injuries. Polytrauma injuries are often associated with exposure to blasts, such as those caused by improvised explosive devices and other

explosive munitions.[35] Blast exposures have resulted in a complex array of outcomes for military personnel, including psychiatric disorders and pain.[9,21] Research evidence suggests that rates of pain and PTSD among OEF/OIF/OND veterans[10,14,21,32] are elevated in comparison to civilian samples,[12,13,18,19,30,33] highlighting the need for comprehensive research and clinical interventions focused on military and veteran populations. Moreover, the comorbidity of pain and PTSD is related to greater affective distress, higher levels of life interference, greater disability, and higher health care utilization than for individuals with either disorder independently.[26,42,44] The high comorbidity and complexity of these conditions complicates the understanding of their etiology, clinical presentation, and treatment.

Etiologic models of pain and co-occurring mental health disorders purport a complex interaction of biological and psychosocial factors. Prevalence of pain symptoms increases with age[8,27] and may also vary among demographic characteristics such as education,[27] socioeconomic status,[1] and gender.[17] Complaints of pain are commonly reported in patients who have experienced traumatic life events, suggesting that lifetime exposure to trauma and stress may be an important risk factor for pain disorders[13,40,44] However, other studies have not fully supported these risk and comorbidity models,[23] suggesting that correlates of pain and stress-related disorders, including PTSD, may not be fully understood. Several theoretical models propose connections between pain and PTSD,[2,9,16,39] which consider the interactive contributions of cognitive, emotional, and behavioral responses that mutually reinforce both conditions. For example, PTSD symptoms may reduce pain tolerance, thereby influencing emotional distress, promoting avoidance behaviors, and increasing perceived disability levels.[2,44] However, less is known regarding the interaction of PTSD and pain symptoms in the context of blast injuries; additional blast-related consequences such as traumatic brain injury (TBI) may complicate the understanding of etiology, assessment, and course of treatment in the context of comorbid pain and PTSD.[35]

Existing work on the co-occurrence of pain and PTSD has primarily relied on cross-sectional prevalence studies, and longitudinal examinations of these conditions are few in number.[12,16,39] For example, although previous work has supported a longitudinal relationship between pain and PTSD symptoms, results regarding the direction of causality[12] and predictive influence of these symptoms over extended follow-up periods[16] have been mixed. Further longitudinal study is needed to provide a more comprehensive understanding of symptom onset and maintenance, particularly within the context of polytraumatic injury, TBI, and military samples.

The lines of research concerning comorbidity, etiology, and longitudinal associations of pain and PTSD have provided a foundation for further work in this area and highlight the need for nuanced analysis of the temporal relationship between pain and PTSD symptoms. The present study investigates the longitudinal course of pain and PTSD symptoms in a sample of active duty military service members and veterans following blast exposure. This study addresses several gaps in the literature by examining longitudinal associations between pain and PTSD symptoms within the context of combat-related blast injuries and by using an autoregressive methodology to examine the temporal associations between these variables and relevant covariates (ie, age, race, injury characteristics). Based on previous research supporting an interactive model of pain and PTSD symptoms, we hypothesized that 1) pain and PTSD symptoms would be significantly associated over time, 2) pain symptoms would predict subsequent PTSD symptoms, 3) PTSD symptoms would predict subsequent pain symptoms, and 4) the relationship between pain and PTSD symptoms would be impacted by the covariates of age, race, and severity of blast exposure.

Methods

Data were collected as part of an ongoing Congressionally Directed Medical Research Program–funded investigation of postcombat injuries from blast exposure during OEF/OIF/OND. Eligible military service members and veterans had a blast experience within the past 2 years while deployed in OEF/OIF/OND. The participants were assessed at 3 time points over a 1-year period: baseline (Time 1 [T1]), after 6 months (Time 2 [T2]), and after 12 months (Time 3 [T3]). The baseline assessment is defined as the time at which the participant entered the study, and the average time between the date of the worst identified blast exposure and the initial assessment period was 519.0 days (standard deviation [SD] = 541.1).

Procedure

The relevant institutional review boards approved this study, and informed consent was obtained after the details of the study were thoroughly explained to participants. All participants completed a series of questionnaires. Although many were enrolled at clinics, the research evaluations were separate from clinical care or compensation and pension processes. Research staff supervised completion of all the questionnaires and provided additional instructions as needed.

Participants

Participants were military service members and veterans recruited via letters, through advertisements, and from ambulatory health care clinics at a mid-Atlantic VA Medical Center and at several Army and Marine Corps bases located in the mid-Atlantic region of the United States. For the present analyses, participants who reported at least 1 blast experience during combat were included in the study (N = 209). The sample consisted of 202 men and 7 women, who were on average 27.4 years of age (SD = 7.6) at the baseline assessment. Many of the respondents reported more than 1 deployment location (Table 1).

Table 1. Descriptive Characteristics of the Sample

	N	%
Sex		
Male	202	96.7
Female	7	3.3
Race		
White/Caucasian	164	78.5
African American	32	15.3
Other race	13	6.2
Deployment location*		
Operation Enduring Freedom		
1 deployment	119	
2 deployments	31	
Operation Iraqi Freedom		
1 deployment	71	
2 deployments	29	
3 or more deployments	10	
Other deployment location	33	
Branch of service*		
Army	88	
Navy	4	
Air Force	2	
Marines	117	

*Note: Some participants endorsed more than 1 response.

Measures

Short Form McGill Pain Questionnaire (SF-MPQ)[22]

Participants were asked to rate current levels of general pain symptoms. This pain rating scale consists of 15 pain descriptors (11 sensory, 4 affective) that are rated for intensity on a Likert-type scale from 0 (none) to 3 (severe). The scale yields 3 pain scores: a total pain score, which is a sum of all 15 items, and sensory and affective pain subscale scores. The total pain score is frequently used in research and clinical applications, with higher scores indicating greater severity of current pain symptoms. The SF-MPQ has been shown to have strong psychometric properties and is sensitive to changes in pain scores over time and/or as a result of clinical intervention.[22] Internal consistency for the total SF-MPQ score in the current sample was good (Cronbach's α = .86).

Prior Health and Demographics Questionnaire

A detailed health and demographics questionnaire was developed for the study. Questions assessed for basic demographic information (eg, sex, age, marital status, race/ethnicity, education, military history) as well as selected psychiatric and medical histories, which were not the focus of the present study. Age was included in the analyses as a continuous variable, and race was categorized as White/Caucasian, African American, or other race. The race variables were dummy coded for analysis, with White/Caucasian as the reference group.

Blast Experience Screening Questionnaire (BESQ)

Participants were queried on their traumatic blast experience(s) via the BESQ, which was developed for a larger epidemiologic study of blast exposures. The BESQ was adapted from the Walter Reed Army Medical Center Blast Injury Questionnaire.[36] The Walter Reed Army Medical Center Blast Injury Questionnaire screens patients for previously unreported blast-related pathologic conditions via 19 questions regarding the blast itself, as well as pre- and postblast symptoms including the presence of visual disturbances, headaches, dizziness, or hearing loss; distance from the blast; and degree of cover. The BESQ focuses on symptoms immediately after the blast exposure and also inquires about alterations of consciousness (AOCs) following the blast. The AOC questions were designed to assess 3 specific aspects of postblast severity: memory gap, observer-reported loss of consciousness, and continuous memory. Respondents are asked to provide information on up to 3 separate blast events, which included a request to identify the "worst" blast event. For the purposes of this study, only information regarding the worst blast event was used to calculate the TBI characteristics. In accordance with previous work with this scale,[45] responses from the selected AOC questions indicating posttraumatic amnesia or loss of consciousness (LOC) were combined to create a categorical index of 3 potential diagnostic groups of mild TBI: definite/probable TBI (2 or 3 positive AOC items), possible TBI (1 positive AOC item), and no evidence of TBI with either posttraumatic amnesia or LOC (all 3 AOC items negative; see[45] for development of the scoring system). The TBI diagnostic classification variables were dummy coded for analysis, with "no evidence of TBI" as the reference group.

PTSD Checklist (PCL)[46]

The PCL is a 17-item self-report measure of the 17 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, symptoms of PTSD. The scale is commonly used to screen individuals for PTSD, aid in diagnostic assessment of PTSD, and monitor change in PTSD symptoms.[25] Respondents are asked, "In the past month, how much have you been bothered by…" each symptom, rated on a Likert-type scale from 1 (not at all) to 5 (extremely). In the current study, the PCL total score was used as a measure of PTSD symptom severity, and the internal consistency in the current sample was excellent (Cronbach's α = .93).

Statistical Analyses

Missing Data Analysis

Of the 209 participants assessed at T1, only 125 completed T2 assessments and 112 completed T3 assessments. Because of substantial attrition, data were explored for patterns in missingness. In addition to exploring potential differences in baseline TBI classification, PTSD symptoms, and pain symptoms as contributing factors to attrition, several demographic variables and military service variables (ie, age, race, deployment location, and military service branch) were also investigated. Missing data at each follow-up assessment period (ie, T2, T3, and missing at both time points) were coded as a

binary variable (1 = missing, 0 = not missing). Preliminary comparisons applied the χ^2 statistic and the F statistic (using the SPSS version 20 Compare Means command; SPSS, Inc, Chicago, IL) for the categorical and continuous variables, as appropriate. These analyses were followed by logistic regression analyses to determine which variables predicted missingness at each follow-up period.

Autoregressive Models

Autoregressive models are also known as Markov simplex or univariate simplex models. These models describe change in a variable over time in terms of the measurement of that variable on previous measurement occasions. A first-order autoregressive model only accounts for the measurement immediately prior to the one of interest. In other words, pain symptoms at time *T* are predicted only by pain symptoms at time $T - 1$, and pain symptoms at any earlier time point have no direct impact on pain at time *T*.[6] Second-order parameters may be added to the model to estimate additional pathways (ie, pain symptoms at time *T* are predicted by pain symptoms at time $T - 2$). A univariate model (ie, a focus on only 1 variable) can then be extended to the multivariate case in order to model 2 or more distinct variables over time. In the present study, pain and PTSD symptoms were first modeled using separate univariate autoregressive models to examine each model's ability to adequately describe the respective symptom scores over time. Pain and PTSD scores at each time point (eg, T2) were regressed onto pain or PTSD scores from the previous assessment period (eg, T1) to determine the extent to which pain symptoms at one time point are predicted by the pain symptoms from the previous 6 months, and the extent to which PTSD symptoms are predicted by PTSD symptoms from the previous 6 months. In other words, the univariate autoregressive model examines how well scores at one time period predict scores at a subsequent time period, thereby illustrating both the degree of change and pattern of change in a particular variable over time. Fit statistics, described below, identified the best-fitting PTSD and pain models before combining the models into a multivariate autoregressive cross-lagged model.

Autoregressive Cross-Lagged Models

The autoregressive cross-lagged model combines separate univariate models and allows the examination of the relationship between multiple processes. For this study, pain symptoms at time *T* were regressed onto pain symptoms at $T - 1$ and PTSD symptoms at $T - 1$, and PTSD symptoms at time *T* were regressed onto PTSD symptoms at time $T - 1$ and pain symptoms at $T - 1$. This multivariate approach allowed us to examine a bidirectional transactional model of pain and PTSD symptoms by testing the extent to which PTSD symptoms are predicted by pain symptoms at the previous 6-month assessment period above and beyond the PTSD symptoms the previous 6 months, and the extent to which pain symptoms are predicted by PTSD symptoms above and beyond pain symptoms the previous 6 months. Fit statistics were used to first identify the best-fitting cross-lagged model before the covariates of age, race, and TBI classification were added to the model. Then, in a final model, the covariates were added to the cross-lagged model to investigate the influence of these factors on the longitudinal associations between pain and PTSD symptoms.

All analyses were conducted in MPlus, version 6.11,[24] using maximum likelihood estimation with standard errors that are robust to departures from normality. Modification indices were examined after each iteration to examine the impact of adding potentially meaningful paths not included in the first-order cross-lagged model and determine the best-fitting models. Only pathways that represented theoretically and/or empirically meaningful relationships were added to the models to reduce the likelihood of nongeneralizable results. In addition to χ^2, fit indices were used to evaluate model fit according to the following criteria: a root mean squared error of approximation (RMSEA) at or below .05,[15] a Tucker-Lewis index (TLI) of .95 or higher,[15] and a comparative fit index (CFI) of .95 or higher.[15] The Bayesian information criterion (BIC)[37] was also used to compare the relative fit of the models. Models with a lower value of the BIC are considered to be better fitting and more parsimonious.

Results

Missing Data

Preliminary exploration of missingness indicated that participants who had missing data at T3 were significantly younger (mean age = 25.8, SD = 6.5) than those who were not missing (mean age = 28.8, SD = 8.3, F[1, 207] = 8.41, $P < .01$). There were no differences in age for missingness at T2 or at both T2 and T3. There were several patterns in missingness related to deployment location history as reported at the baseline assessment: At T2, there were significantly fewer individuals with missing data who reported 2 deployments to OEF, compared to those with 0 or 1 OEF deployment, $\chi^2(2) = 6.58$, $P < .05$. An opposite effect was found at T3, in which those reporting 2 deployments to OEF were more likely to be missing at the final assessment, $\chi^2(2) = 14.4$, $P < .001$. Compared to those deployed to OIF, having a history of no OIF deployments was associated with attrition at T3, $\chi^2(4) = 9.69$, $P < .05$. Compared to individuals in other service branches and with other postdeployment statuses, those who reported service in the Marines and who were on active duty status following deployment were more likely to be missing at T3, $\chi^2(1) = 12.59$, $P < .001$, and $\chi^2(1) = 9.46$, $P < .01$, respectively. Those in the Army and in the Reserves following deployment were significantly less likely to have missing data at T3, $\chi^2(1) = 11.07$, $P < .001$, and $\chi^2(1) = 10.6$, $P < .001$, respectively. The variables of baseline pain symptoms, PTSD symptoms, TBI classification, and race did not demonstrate any significant differences in attrition at T2, T3, or both time points.

The variables with statistically significant patterns of missingness from the preliminary analyses were entered

into a logistic regression analysis in which each follow-up period (ie, T2, T3, both time periods) was the binary dependent variable. At T2, only a history of 2 deployments to OEF contributed significantly to the prediction model, B(SE) = –1.19(.53), 95% CI = .11–.85, exp(B) = .31, $\chi^2 = 7.15$, $P < .05$. At T3, only postdeployment status in the Reserves, B(SE) = –1.22(.58), 95% CI = .09–.93, exp(B) = .30, contributed to the model, $\chi^2 = 27.79$, $P < .01$. None of the variables predicted missingness at both time periods. In sum, the final missing data analysis indicated that those deployed to OEF twice were more likely to have complete data (ie, less likely to be missing) at T2 than those with 0 or 1 OEF deployment, and those in the Reserves postdeployment were more likely to have complete data at T3 than those who were not on Reserve status. Notably, neither pain symptoms, nor PTSD symptoms, nor TBI classification at baseline appeared to be related to attrition, and thus the results of the current study are considered to be an accurate depiction of these symptoms over time.

Descriptive Statistics

Descriptive characteristics of the sample are presented in Table 1. Using the diagnostic classification of TBI based on AOC responses, 45 were considered to have possible TBI and 70 were categorized as probable TBI, with the remaining 94 reporting no symptoms indicative of TBI following blast exposure. All of the PTSD and pain scores were moderately to strongly correlated with each other at the 3 measurement occasions (Table 2). These measures were positively correlated with baseline age. PTSD and pain symptoms were also analyzed for potential differences by TBI classification. For those individuals reporting no symptoms indicative of TBI following blast exposure, the mean baseline total score on the PCL was 45.7 (SD = 15.5) and the mean baseline SF-MPQ total score was 8.8 (SD = 6.7). Among those classified as possible TBI, the mean PCL and SF-MPQ total scores were 47.9 (SD = 15.2) and 12.4 (SD = 8.6), respectively. The mean baseline PCL and SF-MPQ total scores were 50.2 (SD = 13.6) and 13.1 (SD = 8.3), respectively, for those classified as probable TBI. The differences in scores between groups for both the baseline pain symptoms, $F(2, 206) = 7.2$, $P < .001$, and PTSD symptoms, $F(2, 206) = 1.9$, $P = .05$, were statistically significant. At subsequent time points, however, there were no statistically significant differences in pain or PTSD symptoms by TBI classification.

Autoregressive Models

Preliminary analysis of the pain and PTSD symptom scores indicated relative stability and lack of growth in the variables over time. There was not significant change in self-reported pain symptoms over time; however, examination of average PTSD scores showed a slight decrease in symptoms from T2 to T3. Because of the modest growth in the variables, simplex models (ie, autoregressive or Markov models) were considered the best choice to fit the separate pain and PTSD measures. In these initial models, pain and PTSD symptoms, respectively, were regressed onto the symptoms reported at the 6 months immediately preceding. These models resulted in acceptable overall model fit indices (Table 3), indicating that pain symptoms at T1 predicted pain at T2; however, pain symptoms at T2 did not predict pain symptoms at T3. PTSD symptoms at T1 predicted PTSD symptoms at T2, which then predicted PTSD symptoms at T3. The simplex models were included for further analysis in the autoregressive cross-lagged modeling framework.

Autoregressive Cross-Lagged Models

PTSD and Pain-Only Model

The interaction model of pain and PTSD symptoms was evaluated by combining the best-fitting pain simplex model and PTSD simplex model above and adding cross-lagged parameters between pain and PTSD scores. The cross-lagged parameters allowed for an examination of the interaction between variables over time by assessing how well one variable (eg, pain) predicts the other variable (eg, PTSD) at the same or subsequent assessment period. For the initial step, we analyzed pain and PTSD symptom scores without the covariates. The influence of PTSD symptoms on pain symptoms was tested by regressing pain scores onto PTSD scores from the previous 6 months, thereby demonstrating the predictive ability of PTSD symptoms for pain symptoms at the following assessment period. Then, to test for the influence of pain symptoms on PTSD symptoms, cross-lagged parameters were included that regressed PTSD scores onto pain scores the previous 6 months. This resulted in good model fit, $\chi^2(4) = 8.44$, $P = .08$; TLI = .95; CFI = .97; RMSEA = .07 (.00–.14); BIC = 6,607.12. Within-time associations between the pain and PTSD variables were also statistically significant across all time points, $\beta_{T1} = 56.40$, $P < .001$; $\beta_{T2} = 57.81$, $P < .001$; $\beta_{T3} = 25.67$,

Table 2. Correlations Between Age, Posttraumatic Stress Disorder, and Pain Variables

	M (SD)	*1*	*2*	*3*	*4*	*5*	*6*	*7*
1. Age	27.4 (7.6)	—						
2. PCL baseline (n = 209)	47.7 (14.9)	.22**	—					
3. PCL 6 months (n = 126)	47.0 (17.9)	.18**	.65**	—				
4. PCL 12 months (n = 112)	43.9 (16.8)	.40**	.63**	.85**	—			
5. SF-MPQ baseline (n = 209)	11.0 (7.9)	.29**	.48**	.41**	.40**	—		
6. SF-MPQ 6 months (n = 126)	11.8 (8.7)	.25**	.42**	.71**	.65**	.58**	—	
7. SF-MPQ 12 months (n = 112)	11.5 (8.9)	.38**	.39**	.54**	.64**	.45**	.52**	—

Abbreviation: M, mean.
**$P < .001$.

Table 3. Best-Fitting Autoregressive Simplex and Autoregressive Cross-Lagged Models Examining the Longitudinal Relationships Between Pain and Posttraumatic Stress Disorder Symptoms Over a 1-Year Assessment Period

	χ^2	*DF*	P	*CFI*	*TLI*	*RMSEA (90% CI)*	*BIC*	*FP*
Pain simplex	4.62	1	.03	.95	.85	.15 (.04–.31)	1650.08	6
PTSD simplex	.20	1	.66	1.00	1.02	.00 (.00–.16)	1868.29	6
Cross-lagged, combined pain and PTSD*	2.80	3	.42	1.00	1.00	.00 (.00–.11)	6606.96	24
Cross-lagged, combined pain and PTSD with covariates added*†	3.66	3	.30	1.00	.98	.03 (.00–.13)	6678.31	54

Abbreviations: df, degrees of freedom; fp, number of free parameters.
*Cross-lagged models combined pain and PTSD simplex models.
†Covariates included age, race, and traumatic brain injury severity.

$P < .001$, indicating that PTSD and pain symptoms are correlated with one another at a given time point in addition to holding predictive utility for each other at subsequent time points. Modification indices recommended including additional autoregressive parameters for pain measurement at T1 to T3; this resulted in slightly improved model fit, $\chi^2(3) = 2.80$, $P = .42$; TLI = 1.00; CFI = 1.00; RMSEA = .00 (.00–.11); BIC = 6,606.96.

The cross-lagged parameters indicated that PTSD scores predicted pain scores at each subsequent time point, $\beta_{PTSD1\text{-}Pain2} = .10$, SE = .05, $P < .05$; $\beta_{PTSD2\text{-}Pain3} = .15$, SE = .06, $P < .05$. However, pain at T1 only predicted PTSD at T2, $\beta = .36$, SE = .14, $P < .05$. The parameter between pain at T2 and PTSD at T3 was not statistically significant, $\beta = .07$, SE = .18, $P = .67$ (Fig 1).

Covariate Model

Finally, we included the covariates of baseline age, race, and TBI classification in the cross-lagged model. This model resulted in good fit, $\chi^2(3) = 3.66$, $P = .30$; TLI = .98; CFI = 1.00; RMSEA = .03 (.00–.13); BIC = 6,678.31; however, the model fit indices decreased somewhat from the previous model. As with the previous model, modification indices recommended the addition of a second-order cross-lagged parameter from pain scores at T1 to pain scores at T3 (Fig 1). The covariates were not statistically significant for all parameters. The covariate model indicated the same associations between the pain and PTSD variables as the initial cross-lagged model, and this final model is illustrated in Fig 1. The results suggest that the inclusion of covariates, though clinically meaningful and potentially theoretically important, did not add significant explanatory power to the overall model.

Discussion

This is the first study to examine the longitudinal interactive effects of pain and PTSD symptoms in a military/veteran sample using an autoregressive cross-lagged design. The autoregressive cross-lagged model is a powerful method for exploring the temporal association of 2 variables over time. Overall, results are consistent with the literature supporting a strong relationship between pain and PTSD symptoms.[16,21,39,44] The longitudinal nature of the data allowed us to

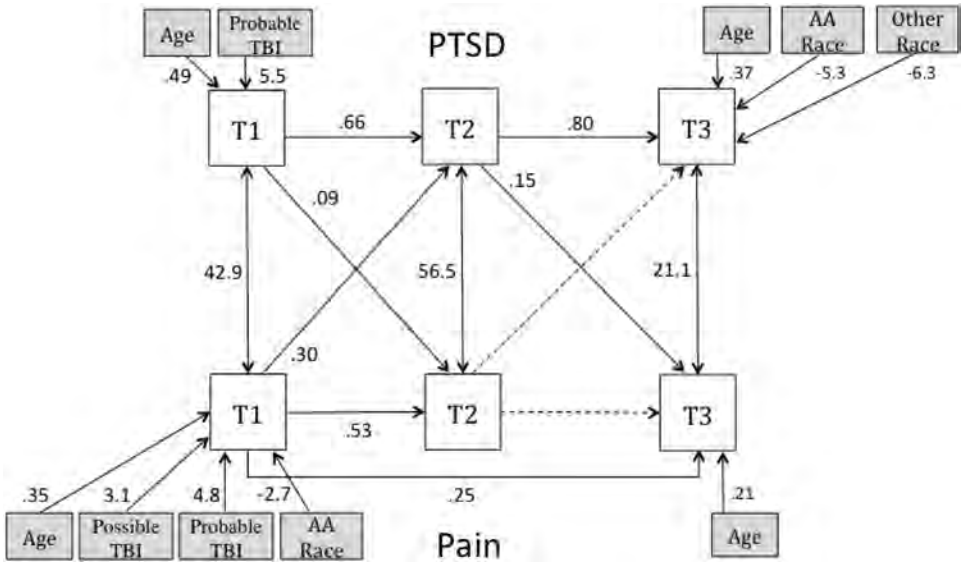

Figure 1. Best-fitting autoregressive cross-lagged model with covariates included. Solid lines represent significant ($P < .05$) standardized regression estimates. Broken lines represent paths that were included in the model but were not statistically significant. Only the statistically significant pathways for the covariates of age, race, and TBI injury status are illustrated in this figure.

investigate natural interactions of symptoms over time, and the results yielded important insights into the relationship between pain and PTSD symptoms in the context of combat-related blast exposure. A better understanding of pain and PTSD symptom maintenance is particularly important for the assessment and treatment of military personnel who have experienced polytrauma injuries and who are at risk for long-term complications as a result of this complex injury profile.

When first considering pain and PTSD symptoms separately, we found that the reported symptoms were relatively consistent across time. Notably, pain scores at T2 and T3 were independently predicted by pain at T1, suggesting that initial pain and/or injury status may be the most important indicator of future pain symptoms. Similar results have been found in other pain samples, in which disability status, pain-related distress, and comorbid psychiatric or personality factors at time of injury have been shown to predict chronicity of pain symptoms, for example.[7,29,41] Despite PTSD symptoms showing a slight decrease over time, on average, the autoregressive cross-lagged models demonstrated that PTSD scores were best predicted by PTSD scores the previous year, as indicated by the large parameter estimates of the autoregressive portion of the model. Thus, although recovery from PTSD symptoms is a common trajectory following trauma exposure,[4,5] many participants in our sample continued to be affected by significant PTSD symptoms at the 12-month assessment period, as evidenced by average PCL scores that fell within the range of suggested PTSD diagnostic cut-offs (the suggested cut-off for specialized VA primary care clinics and specialized TBI or pain clinics is 36–44).[25] It is important to note that our assessment period was limited to 1 year, and there is evidence that spontaneous PTSD recovery may take several years before symptoms significantly remit.[4,5] The stability of both the pain and PTSD symptoms may also be related to the amount of time between the initial injury and the study's baseline assessment period (approximately 17 months, on average). Symptoms may have had ample time to stabilize and/or become chronic presentations. A shorter injury-to-assessment period and a longer follow-up period of PTSD and pain symptoms will add clarity to the longer-term trajectory of postcombat difficulties.

Consistent with our expectations, we observed significant associations between pain and PTSD symptoms over the 3 assessment points. Pain and PTSD symptoms showed strong within-time correlations in the cross-lagged model. Further, PTSD scores at T1 significantly predicted pain scores at T2 and T3, above and beyond the previous pain scores. Pain predicted PTSD scores above and beyond the previous PTSD scores at T2 but not at T3. The findings suggest that although pain and PTSD appear to interact and influence one another over time, PTSD appears to exert a particularly strong influence on pain scores. Jenewein and colleagues'[16] longitudinal study of PTSD and pain symptoms among accident survivors similarly found a mutual maintenance of pain intensity and PTSD symptoms over a 6-month period, but at 1 year, PTSD symptoms were demonstrated to have a significant impact on pain symptoms, whereas pain symptoms were no longer shown to have a significant impact on PTSD symptoms. The interactive model of pain and PTSD is supported by theoretical conceptualizations of the co-occurring disorders,[2,38] and our findings lend empirical support to these conceptual models. In particular, PTSD symptoms appear to have a significant impact on pain symptoms. This finding has important theoretical and clinical implications, as symptoms associated with PTSD may prolong comorbid pain, thereby contributing to the chronicity of both presentations and preventing effective rehabilitation. Common behavioral or psychosocial factors, such as hypervigilance to perceived threats and withdrawal from rewarding daily activities, may be an important link between the 2 conditions.[12] Our results suggest that a focus on PTSD symptoms may be an important first step in complementary treatment interventions, as these psychological and behavioral factors appear to influence future pain symptoms. Interventions for the co-occurring disorders may emphasize treatment of PTSD symptoms and consistent, ongoing monitoring of psychological symptoms in order to effectively reduce the long-term difficulties associated with both presentations. Particularly among military personnel, pain complaints may be more commonly reported or viewed as more socially acceptable than PTSD symptoms or other mental health difficulties, and clinical service providers may miss important potential underlying psychological and behavioral contributions to pain.

Finally, we investigated the influence of selected covariates on the interactional model of pain and PTSD symptoms. Older age at the baseline assessment was associated with both pain and PTSD symptoms at T1 and T3, a finding that is largely consistent with previous work on pain and comorbid disorders, for example.[8,27,34] White/Caucasian race was related to pain symptoms at T1 and to PTSD symptoms at T3, which is contrary to prior studies suggesting that minority race/ethnicity individuals may be at increased risk for both disorders.[11,20,28,31] Notably, our sample was chiefly composed of individuals who self-identified as White/Caucasian, and thus there may not have been sufficient power to detect true differences between the race groups and relationships to the symptom variables. Future work with more diverse and representative samples is needed to clarify these associations. The final model also indicated that more severe TBI diagnostic classification status (ie, probable and possible TBI) was associated with more severe pain and PTSD symptoms at T1. Although the study did not explicitly query for pain or PTSD symptoms related to blast injury, the demonstrated relationship between TBI classification status and symptoms suggest that the blast event has an important additive (if not directly causative) effect on subsequent physical and psychiatric symptoms. This finding highlights the relevance of the initial injury period to the early stages of polytrauma complaints, as TBI and blast-related symptoms may function as important indicators for identifying those individuals who go on to develop more chronic symptoms. Although the final covariate autoregressive cross-lagged model showed good fit, the covariate model did not demonstrate significant improvements

over the model investigating pain and PTSD symptoms alone. Thus, the demographic and injury characteristics of our sample appeared to have a primary influence on initial assessment of pain and PTSD symptoms in our sample, and the interactive relationship regarding pain and PTSD best explained the longitudinal symptom maintenance in our sample.

There were several limitations to this study that must be noted. First, autoregressive cross-lagged models are only one of several methods for examining relationships between variables over time. We selected this model because it allowed us to examine the extent to which symptoms of one disorder (eg, pain) are predicted by earlier symptom reports of co-occurring symptoms (eg, PTSD), above and beyond previous reports of pain symptoms. This method does not model growth across all time periods, nor does it consider individual differences in the trajectories of pain and PTSD over time. Combined autoregressive and latent growth curve models have the benefit of modeling time-specific changes in symptoms while taking into account individual growth trajectories.[6] However, we were unable to examine these models because of the relative stability (and, thus, absence of significant latent growth factors) for both symptom measures. Another limitation of the study was the attrition rate from baseline to the final assessment; approximately 46% of the original sample did not complete the 12-month assessment. Although missing data analysis did not determine any significant differences in our sample with regard to baseline pain and PTSD symptoms or TBI classification, and our final sample size was adequately powered for the autoregressive modeling framework, more complete data may yield additional findings and insights into comorbid pain and PTSD symptoms and the influence of relevant covariates. Interestingly, missing data analysis found that those participants who reported 2 OEF deployments were more likely to be Marines and on active duty status post deployment, whereas those individuals in the Reserves were almost predominantly from the Army. These groups were more likely to have complete data at the T2 and T3 follow-up periods, respectively. Although redeployment status and service transitions throughout the assessment periods were not assessed, it may be possible that individuals in the Reserves were less likely to be reactivated for duty or deployment and therefore more likely to be available for participation in the final assessment period. Similarly, the timing of the T2 assessment may have coincided with deployment schedules such that those with multiple OEF deployments happened to be more readily available for the second assessment.

Further, this study relied on self-reports of pain, PTSD, and TBI symptoms. Although self-report assessments can be helpful for assessing an individual's perceptions of distress and difficulties, a limitation of this assessment method is the potential bias in the respondents' self-report of their past experience and symptoms. Moreover, information regarding predeployment medical and psychiatric conditions was limited for our sample, and it is unknown whether the reported symptoms indicated new complaints or exacerbations/continuations of existing difficulties. Thus, although this study was able to identify patterns of symptom co-occurrence and mutual maintenance, factors related to symptom onset are less clear; this is a target for future study. We decided to focus on the comorbidity of pain and PTSD symptoms for the present analyses, but it is well known that pain is also highly associated with depression symptoms.[3,43] Future work will investigate the influence of depression on both pain and PTSD symptoms, as this may represent an additional variable that accounts for maintenance of these co-occurring presentations. Finally, the study sample of relatively young, primarily male military service members and veterans reflects a particular composition of military personnel, and the findings may not generalize to the general population or other military/veteran samples. More work is needed to better understand the risk factors and correlates of pain in diverse samples.

In summary, these findings hold important implications regarding clinical interventions for pain and co-occurring psychiatric and medical symptoms in returning service members and veterans. These data indicate an extensive number of returning OEF/OIF/OND military personnel and veterans with polytraumatic injuries who continue to be affected by these symptoms many months following blast exposure. A strength of the present study is the investigation of longitudinal outcomes and comorbidity patterns using a robust data analysis methodology that is well equipped to determine the interactive relationships between symptoms. Findings from the present study demonstrate that postdeployment symptoms strongly influence one another and interact across time, and PTSD symptoms appear to exert a strong influence on subsequent pain symptoms. Given that pain and PTSD symptoms co-occur frequently and influence one another, it is important to identify both pain and PTSD symptoms in clinical assessment and treatment planning processes. Early clinical interventions and rehabilitation efforts may consider the treatment of both pain and psychiatric symptoms in hopes of optimizing treatment and decreasing the probability that symptoms will persist and become chronic psychological or physical responses to trauma.

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Title: Diagnostic accuracy of PTSD Checklist in blast exposed military personnel

Running Title: PTSD Checklist accuracy after blast exposure

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Abstract:

Researchers often extrapolate post-traumatic stress disorder (PTSD) status from PTSD Checklist (PCL) data. When doing so, cut scores should be based on samples with similar characteristics. This study assessed PCL diagnostic accuracy and post-concussive symptom levels within 106 Iraqi/Afghanistan War Veterans and Service Members with recent blast exposure. Two definitions of PTSD were applied: 1) "strict" Diagnostic and Statistical Manual of Mental Health Disorders 4th edition (DSM-IV) criteria and 2) "relaxed" DSM-IV criteria dropping the A2 criterion as per DSM-V. Using structured interview for PTSD, we found moderate agreement with the PCL. Under strict criteria, PTSD prevalence was 16%, PCL cut score was 66 at peak *kappa*, and mean Rivermead Postconcussion Questionnaire (RPQ) score trended higher for those with PTSD (35.5 +/- 11.2 versus 30.5 +/- 10.7, p=0.080). Under relaxed criteria, PTSD prevalence was 26.4%, PCL cut score was 58 at peak *kappa*, and those with PTSD had higher RPQ scores (36.4 +/- 11.2 versus 29.5 +/- 10.2, p=0.003). Participants diagnosed with blast-related mild traumatic brain injury (mTBI) (n=90) did not differ from those without mTBI (n=16) in symptom scores. In conclusion, persons with combat-related blast exposure need higher than conventional PCL cut-points, and those with PTSD have more severe post-concussive type symptoms.

Introduction:

Exposure to psychologically traumatic events is an inherent aspect of military combat deployment and often may lead to post-traumatic stress disorder (PTSD). In Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND), U.S. Service Members (SMs) have experienced an especially high rate of exposure to blast-induced traumatic events. Heavily used by the insurgents, explosive munitions have accounted for about 78% of wounded in action cases, the highest proportion for any large scale conflict (1). Accordingly, OEF/OIF/OND combatants are typically screened for PTSD after returning from deployment, usually via the easy-to--administer and widely used PTSD Checklist (PCL) (2, 3). The PCL is favored by both the U.S. Department of Defense (DoD) and the Veterans Health Administration (VHA) as a PTSD screening tool and is mandated in certain clinical settings.

Although not intended as a diagnostic tool, numerous published clinical research studies have used the PCL to categorize individuals into PTSD positive versus negative groups, typically using a total score >= 50 to define PTSD (4). But most studies, particularly those focusing on mild traumatic brain injury (mTBI) cohorts, have used the PCL in this manner without fully considering its diagnostic accuracy and optimal cut score within their sampled population (5). The accuracy of any diagnostic tool, such as sensitivity and specificity values, is heavily influenced by the true prevalence of the index condition within the population under study. Regarding PTSD, the entire post-deployment population does not have uniformity of traumatic exposures and risk level. Exposure rates to blast and other traumatic combat events vary widely depending on one's military role and deployment specific geographic location and missions (6). Therefore the true prevalence of PTSD will vary with different sample selection methods, which in turn impacts the diagnostic accuracy of the PCL. Therefore, it is unlikely that commonly accepted Veterans population cut-points (e.g. 50) (2, 7) would be equally

appropriate across different population types or study samples. The population of blast-exposed SMs and Veterans is a key target population because they are most at risk for the signature wounds of OEF/OIF/OND, TBI and PTSD, and are the focal point of VA and DoD clinical care and research efforts. But the literature lacks guidance on how to categorize PTSD in this very high risk population using the PCL.

Current warfighters and the situations they face are different than those faced by the original validation samples for the PCL (Vietnam and first Gulf War combat veterans). Now, new stressors may be involved in the development of PTSD – "exponentially" more and much longer deployments, improvised explosive devices (IEDs) and suicide bombers, exposure of peacekeeping forces to combative situations, and higher survivability of wounds (8). The potential for TBI is also a critical consideration that may confound PTSD determinations within the military and Veterans population. Over 266,000 TBI casualties have been reported by the DoD between 2000 and 2013 (9), and concussion, aka mTBI, accounts for well over 80% of these (10). Importantly, up to 20% of persons sustaining mTBI will develop Post-Concussion Syndrome (PCS), a condition of chronic symptoms and potential psychosocial dysfunction (11, 12) that has significant symptom overlap with PTSD. Because of this symptom overlap, the presence of PCS after mTBI may inflate the PCL score and generate higher rates of false positive PTSD screens if standard cut points are used. While PTSD symptoms are reported to occur acutely in up to 40% of U.S. military personnel following an mTBI (13), and persistently in 42% of recent OEF/OIF Veterans with a history of mTBI (14), the actual PTSD risk and prevalence among those who sustained mTBI during OIF/OEF/OND is unknown because these and other investigations have determined PTSD status from PCL cut-points that were derived from much different samples of combat Veterans, notably without high mTBI prevalence. For example, Kontos et al (15) reported that military personnel with a self-reported blast-related mTBI diagnosis were at risk (odds

ratio 4.2 versus no mTBI diagnosis) for reporting "clinical levels" of PTSD symptoms, but this was defined as a cut score >= 28 on the PCL which was not cross-validated for clinical PTSD.

The specific PCL scoring method used will also influence its diagnostic accuracy. Some investigators have proposed using a symptom categorization method rather than total score to categorize study participants. The *symptom cluster method* (SCM) requires the endorsement of one re-experiencing, three numbing/avoidance, and two hyperarousal symptoms as per DSM-IV-TR diagnostic criteria (16). A combination of the total score and SCM has also been proposed and used ostensibly to enhance specificity and positive predictive power (PPP) by raising the symptom severity threshold of SCM alone (17).

Because of these sampling and scoring issues, published PTSD prevalence rates among SMs and Veterans with OEF/OIF/OND combat deployment histories have shown widely varying rates from 1.4% to 31% (4). Moreover, almost all studies in the past two decades have relied on DSM-IV criteria to base their gold standard PTSD definition, which may not correlate well with the recently released DSM-V criteria. It will be important for future studies using legacy data to impute their findings into this emerging standard.

In summary, the present study was undertaken because much remains to be learned about the influence of mTBI on PTSD and PCS symptom reporting and on the diagnostic accuracy of the PCL among persons with military blast exposure. The current study is part of an overarching research project aiming to comprehensively assess individuals with one or more combat-related blast experience, defined as a blast event that they were proximate to and felt some immediate physical effect. Such individuals are believed to be at very high risk for not only TBI but also PTSD and are typical of former OEF/OIF/OND combatants seeking care or evaluation for TBI within the DoD or VA. We first sought to determine the true prevalence for the diagnosis of PTSD within this high risk study sample using

structured interview as the reference standard for PTSD. Because the diagnostic accuracy of the PCL is not well established for such a population, we also sought to assess its accuracy across cut-points and determine the optimal method for dichotomizing the PCL into PTSD diagnoses. Thirdly, we aimed to assess what effect the exclusion of the DSM-IV A2 criterion (emotional reaction to stressor) might have on these findings because this method has been advocated for combat experiences and is more consistent with DSM-V. Lastly we sought to determine the relationship between the diagnoses of PTSD and blast-related mTBI to current PTSD and PCS symptom levels.

Methods:

The study sample was 106 consecutive participants who consented and completed baseline evaluations after structured interviews were added to the parent epidemiologic study of military blast exposure in 2010. All appropriate institutional review board and governmental approvals were obtained. SMs and Veterans were eligible if they had a blast experience within the past two years while deployed in OIF/OEF/OND. Participants were recruited via letters, advertisements, and from ambulatory health care clinics at the Hunter Holmes McGuire VA Medical Center (VAMC) in Richmond, VA, Fort Lee Army Base in Prince George County, VA, Quantico Marine Corps Base (MCB) in Prince William County, VA and Camp Lejeune MCB in NC. Blast experience was defined as having any of the following symptoms or experiences occurring during or shortly after exposure to blast or explosion: dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, or medically evacuated. Individuals with severe or moderate TBI were excluded, so participants either had no TBI or sustained an mTBI during their blast experience. Severe or moderate TBI was defined as: more than 30 minutes of lost

consciousness, brain bleeding or blood clot (abnormal brain CT scan), or amnesia for the first 24 or more hours after event.

As part of a comprehensive baseline assessment battery all participants completed the PCL and the Rivermead Postconcussion Questionnaire (RPQ). We used the civilian version of the PCL, in which items are identical items to the military version, to avoid assuming only military-related traumatic life events had occurred. The RPQ is a 16-item self-report measure of the presence and severity of the 16 most commonly reported post-concussion symptoms found in the literature as compared to pre-traumatic event (18, 19). Subsequently and separately, trained research assistants who were blinded to the PCL results administered to each participant the structured interview battery consisting of the Events Checklist for Military Personnel (ECMP), the Mini-International Neuropsychiatric Interview (MINI) version 6.0, and a diagnostic TBI interview.

The ECMP is a questionnaire developed specifically for this study that was used to identify distressing combat and non-combat events that met the DSM-IV Criterion A for PTSD (qualifying stressor). The ECMP differs from other traumatic events questionnaires (20, 21) in that items pertaining to combat events are listed separately from non-combat events. For each list, respondents are first asked to mark whether each event occurred (e.g., "Witnessed the serious injury or death of enemy troops"). Next, they are asked to identify which event "was the MOST distressing or traumatic," the date, their age, and a series of questions regarding their response to the event (e.g., fear, helplessness, or horror; anger), the intensity of distress at the time of the event and at the time of the rating (8-point scale from "not at all" to "extremely"), and the outcome (e.g., "Were you physically injured during the event?"). Finally, respondents are asked to identify whether a combat or non-combat event was the most traumatic event ever experienced.

The MINI is a validated short structured diagnostic interview based on DSM and ICD criteria that was developed by psychiatrists and clinicians jointly in the United States and Europe (22). The MINI has been validated against the Structured Clinical Interview (SCID) and the Composite International Diagnostic Interview with good concordance (22). In comparisons of the MINI and the SCID for the diagnosis for PTSD, Sheehan et al. (22) reported a sensitivity of .85, specificity of .96, positive predictive value (PPV) of .82, negative predictive value (NPV) of .97, and kappa of .78. More recently, Jones et al. (23) found high concordance between the MINI and the SCID and recommended the MINI as a shorter, standardized interview for Axis I diagnoses. When this study was initiated, the 4th edition of DSM was the current gold standard upon which the MINI was based. In order to better inform whether or not the A2 criterion was met, we added structured follow-up questioning if the participant denied that the most distressing event was followed by "an emotional reaction characterized by intense fear, helplessness, or horror". Specifically, if the initial query response was "no" then the participant was also asked to 1) "describe the emotion" if any, and 2) "were you stunned or shocked in a way that you didn't feel anything at all?" followed if yes by querying again whether the A2 emotional response occurred "after the event had passed." Interviewers received workshop training given by a member of the MINI development staff followed by *in vivo* practice vignettes, rating of three practice video tapes, and fidelity evaluation by a licensed clinical psychologist (S.M.).

From the MINI information, each participant's PTSD diagnosis was determined using both a "strict" DSM-IV algorithm and a "relaxed" DSM-IV algorithm. The algorithms were identical except the strict required the DSM-IV A2 criterion to be met while the relaxed ignored A2 so as to simulate DSM-V. For those participants initially negative for the A2 structured question but who either had another strong emotion or a delay in A2 after an immediate "numb" period, the study investigators made the A2 determination after reviewing the written descriptions.

The diagnostic interview for TBI was developed by the study investigators and was administered by a trained research assistant and consisted of both structured and unstructured components. For those with multiple blast-related experiences, the self-identified "worst" potential concussive event was selected for interview. The structured component focused on recalled immediate post-event symptoms that suggest alteration of consciousness occurred (e.g. amnesia, loss of consciousness, dazed, confused, saw stars) and queried for other post-event symptoms (e.g., headache, dizziness, irritability, fatigue, or poor concentration). Responses were independently reviewed by several experienced TBI physicians who individually rated each participant's worst (or only) blast exposure as Yes versus No in reference to the DoD/VA common definition for mTBI (http://www.healthquality.va.gov/mtbi/concussion_mtbi_full_1_0.pdf). Under these guidelines, determining that an immediate period of altered consciousness occurred is essential to diagnosing mTBI pursuant to an injury force; other post-injury symptoms can be used to support, but cannot be used to make, a diagnosis of mTBI in adults. A consensus diagnosis was obtained for each participant based on a simple majority.

History of mTBI prior to military service, prior deployments, and number of blast experiences were also collected using a modified version of the Walter Reed Army Medical Center Blast Injury Questionnaire (WRAMC BIQ), described by Scherer et al (24).

Statistical Methods:

Using the MINI to categorize the PTSD positive and negative status groups under both criteria, we performed between group analyses with respect to their PCS symptom severity (RPQ) and PTSD symptom severity (PCL). We also compared PCL scores and RPQ scores for mTBI versus not TBI groups. All statistical analyses were conducted using SPSS Statistics version 21.0 (IBM SPSS). If variables were normally distributed (i.e., Shapiro-Wilk P value>.05) then independent-sample, unpaired,

two-tailed t-tests were conducted to assess for differences between groups. The Levene test for the equality of variances was calculated, and if the significance was found to be less than .05, equal variances were not assumed. For variables not normally distributed, we used the non-parametric Mann-Whitney U test for comparing independent samples.

Sensitivity, specificity, and area under receiver operating characteristic curves were calculated using SPSS Statistics version 21.0. Other diagnostic accuracy indices (e.g., *kappa*) and Wald 95% confidence intervals (25) were calculated using commonly available spreadsheet software. Using STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines (26), we next analyzed the diagnostic accuracy of the PCL for both MINI algorithms and the two PCL scoring methods. Classification metrics computed were sensitivity, specificity, positive predictive power (PPP), negative predictive power (NPP), percent correctly classified, and kappa statistic of the PCL using different PCL scoring methods and for both strict and relaxed DSM-IV criteria. To determine the optimal cut score for each condition, the diagnostic accuracy parameters were inspected at every cut score. Classification rate and *kappa* were both considered when considering the cut score with optimal diagnostic accuracy. The PCL SCM under DSM-IV PTSD criteria is positive if person endorses at a level of moderately or higher (3, 4, or 5) at least 1 intrusion symptom (Q1-Q5), at least 3 avoidance symptoms (Q6-Q12), and at least 2 hyperarousal symptoms (Q13-Q17) (5). For the PCL total score method we analyzed overall diagnostic accuracy from the receiver operating characteristic (ROC) curve and inspected diagnostic accuracy parameters at each coordinate (cut-point). Confidence intervals (95%) were computed for all diagnostic accuracy fractions using the Wald method (25).

Results:

Participant Characteristics:

The demographic characteristics of the study sample (n=106) are displayed in Table 1. To summarize, participants were evaluated at a median of 15.1 months (interquartile range (IQR) = 10.1 – 24.4) after their worst blast experience and 12.9 months (IQR = 8.0 – 19.9) after the most recent of their three reported worst blast experiences. The vast majority (n=90, 84.9%) were determined to have sustained an mTBI during their worst blast experience.

Insert Table 1 around here

Psychologically Traumatic Events Experienced

All participants reported at least one psychologically traumatic event during combat tour and most (85.7%) also reported at least one traumatic event outside of combat tour. Regarding their "most" psychologically traumatic event, 91 participants reported that it was a combat event which occurred at a median age of 23 years (IQR = 20.5 – 26.0). The remaining 15 participants (13.2% of total sample) reported that a non-combat event was their most traumatic; these occurred at a median age of 19 years (IQR = 15.0 – 23.0). The specific types of events and frequencies are displayed in Table 2.

Insert Table 2 around here

Prevalence of PTSD in sample:

The implementation versus non-implementation of DSM-IV Criteria A2 had significant bearing on the true PTSD prevalence rate derived from the MINI. The prevalence rate was 16.0% (17/106) under the strict algorithm and was significantly higher at 26.4% (28/106) under the relaxed algorithm (McNemar's test of symmetry, p = 0.001). Among the 11 participants meeting relaxed but not strict criteria, 3 participants reported having no strong emotional response and 8 participants reported some "other" strong emotional responses: "anger" by four and by one each "adrenaline", "training kicked in", "respect", and "disgust." The PTSD prevalence was not influenced by mTBI status (PTSD relaxed criteria prevalence if yes TBI = 26.7% versus if no TBI = 25%, Pearson Chi Square, p=0.889 (ASE=0.045); PTSD strict criteria prevalence if yes TBI = 26.7% versus if no TBI = 26.7%, Pearson Chi Square, p=1.00 (ASE n/a).

PCL total score and RPQ-16 score subgroup analyses

The results of analyses of PTSD and PCS symptom severity between PTSD positive and negative groups on the MINI under both criteria are displayed in tabular form in Table 3and Table 4. When applying the strict (A2 inclusive) DSM-IV criteria, those with PTSD (n=17) had higher mean (SD) PCL total score than those without PTSD (n=89), 62.4 (11.0) versus 45.9 (14.03), t=5.86, p < 0.001, *d*=1.22; and trended toward higher RPQ scores, 35.5 (11.2) versus 30.5 (10.7), t = 1.77, p = 0.080, *d*=0.46. When dropping the A2 criterion, those with PTSD (n=28) again had significantly higher PCL scores than those without PTSD (n=78), 61.0 (11.6) versus 44.0 (12.0), t = 6.50, p< 0.001, *d*=1.43; and had significantly higher RPQ scores, 36.4 (11.2) versus 29.5 (10.2), t = 2.98, p = 0.003, *d*=0.66.

Insert Table 3 and Table 4 around here

The additional between group analyses are not shown in tabular form. When comparing the two PTSD positive groups under Strict DSM-IV criteria (n=17) versus Relaxed DSM-IV criteria (n=11), there was no difference in mean PCL scores, 62.4 (11.0) versus 58.9 (12.6), p=0.517, *d*=0.30; as well as no difference in RPQ scores, 35.5 (11.2) versus 37.6 (11.6), t= -0.479, p= 0.636, *d*=0.18.

Comparative PTSD and PCS symptom severity between mTBI positive versus negative groups was also analyzed. Mean (SD) PCL total scores did not differ between participants with historical blast-related mTBI versus without it; 48.9 (13.9) versus 46.4 (15.3) respectively, p=0.494, *d*=0.18. Likewise Mean (SD) RPQ scores did not differ between the mTBI positive and negative groups; 31.3 (10.5) versus 31.3 (12.9), p=1.00, *d*<0.01.

Given our findings that PCS symptoms were influenced by having PTSD, we removed PTSD positive participants (relaxed criteria) and performed further explorative symptom severity analyses within the exclusively PTSD negative subgroup (n=78). In this group, mean (SD) PCL scores again did not differ between the mTBI positive (n=12) and negative (n=66) participants; 42.3 (13.9) versus 44.3 (11.7), p=0.95, *d*=0.17. Within this sub-group, mean (SD) RPQ scores also did not differ between the between mTBI positive and negative participants; 29.5 (9.7) versus 29.3 (13.1), p=0.95, *d*=0.02. However, we did find within this PTSD negative sub-group that mean (SD) RPQ scores trended towards higher scores among those with multiple blast exposures (n=61) versus a single exposure (n=17); 30.6 (9.6) versus 25.5 (11.6), p=0.07, *d*=0.51. Those with multiple blast exposures also had higher PCL scores; 45.6 (12.0) versus 38.3 (10.5), p=0.03, *d*=0.63.

Diagnostic Accuracy of PCL:

For the PCL total score method, the diagnostic accuracy was analyzed for both the strict (A2 inclusive) DSM-IV criteria and the relaxed (not requiring A2) DSM-IV criteria. Overall, the ROC curve's area under the curve was similar for each of the analyses (.83 for each).

The accuracy values and their 95% confidence interval (CI) for the full range of cut-points under strict criteria are shown in Table 5. At 16.0% PTSD prevalence and ignoring CIs, a cut score of 66 provided the peak *kappa* value (.49) as well as the peak correct classification rate (87%). This cut score offered high specificity (.93) and NPP (.91) but lower sensitivity (.53) and PPP (.60). The calculated prevalence of PTSD at this cut score was near the true prevalence (14% vs. 16%). The cut scores that generated the most accurate prevalence rates were 64.5 (15%) and 63.5 (17%).

Insert Table 55 around here

Accuracy data with CIs across cut-points using the relaxed criteria are shown in Table 6. At a native 26.4% PTSD prevalence, a cut score of 58 provided the peak *kappa* value (.54), a fairly high classification % (.81), and a slight overestimate of PTSD prevalence (30.2%). At this cut score and at a 26% PTSD prevalence, the PCL tended to favor the minimizing of false positives (37%; 1 - PPP) over false negatives (11%; 1 - NPP). Ignoring CIs, a cut score of 66 provided the peak classification % (.82) but *kappa* (.46) was below peak (.54). It also generated a significant underestimate of PTSD prevalence

(14.2%) such that its entire 95% C.I. (09% – 22%) was below true prevalence (26.4%). Not considering CI, a cut score of 60.5 generated the most accurate prevalence rate at 25%.

Insert Table 6 around here

Next, the diagnostic accuracy of the PCL using the SCM was examined. Across the three analyses (strict criteria, relaxed criteria, and strict criteria with 26.42% prevalence), classification % and *kappa* were considerably lower than had been produced by the total score method at the optimal cut-points (see Tables 5 and 6).

We had intended to also analyze a combined SCM and total score scoring method, but all participants with a PCL total > 48.5 were SCM test positive except for one SCM negative subject with a total = 56 who was MINI negative. Requiring positivity on both methods would not enhance specificity since the SCM failed to correctly reclassify any of the 10 total score false positive misclassifications under relaxed criteria at its best-performing cut-point. Hence we abandoned further analysis of combining the two scoring methods.

Discussion:

In examining the diagnostic accuracy of the PCL, we began by calculating the true prevalence of PTSD in this high risk sample. Among these blast exposed and predominantly mTBI positive Veterans

and SMs, the prevalence rate for PTSD was 16.0% under strict adherence of DSM-IV criteria, but jumped to 26.4% with removal of the A2 criterion that stipulates having a subjective immediate response of "intense fear, helplessness, or horror". The A2 criterion has been criticized for weak association with developing clinical PTSD, and hence was removed in the recently released DSM-V criteria (27). Calhoun et al (28) has previously predicted that the PTSD prevalence rate would rise under DSM-V criteria for samples that have rates below 50% under DSM-IV criteria. This prediction was primarily based on the changes to the symptom cluster criteria rather than the A2 criteria given that 97% of Calhoun's sample meeting A1 also met A2. Importantly, Calhoun's study sample was predominantly civilian with only 15% reporting combat related stressful events. Thus, our study findings of a large increase in prevalence when removing the DSM-IV A2 criterion suggest that migration to DSM-V will have a greater impact on military and veterans samples relative to civilian samples.

Other investigators have noted that by limiting the subjective response to immediate "intense fear, helplessness, or horror," the A2 criterion does not adequately describe the experience of military personnel in combat who develop clinical PTSD. For example, in a sample of U.S. soldiers returning from combat deployment in Iraq, Adler et al reported that 16% of those with combat-related A1 events did not also endorse the A2 criterion but nonetheless had significant PTSD symptoms warranting further clinical evaluation (29). Our finding that removal of A2 did not change mean PCL scores for those otherwise DSM-IV positive adds to the mounting evidence that A2 criterion lacks clinical utility in military and Veterans populations. It appears that, for many military combatants the immediate strong emotional response is suppressed and/or the total combat experience accounts for persisting PTSD symptoms rather than a specific event. Bliese et al(30) chose to remove A2 from their structured interview since they noted that many soldiers did not endorse A2 reactions but instead reported reactions such as "my training kicked in" or "I was angry" when asked how they reacted to combat experiences.

We found similar responses among our participants when queried for "other strong emotions" if negative for "intense fear, helplessness, or horror." Thus, our findings provide further evidence that removal of the DSM-IV A2 criterion is preferred for combat experiences and that published PTSD prevalence rates are likely to climb after the adoption of DSM-V, at least as compared with studies having used strict DSM-IV criteria in similar high risk post-deployment samples.

Moreover, if military samples are affected by the symptom cluster changes to DSM-V in a fashion similar to Calhoun's study (28), our study findings may be underestimating the projected rise in formal prevalence rates for military samples. This is because we used a DSM-IV version of structured interview and so did not assess for the influence of the DSM-V changes to the symptom cluster criteria. In addition to changing the clusters from 3 to 4, DSM-V adds 3 new items not assessed for in the present study (31).

Interestingly, we found that a history of sustaining a blast-related mTBI did not alter the prevalence of PTSD, the severity of PTSD like symptoms, or the severity of PCS symptoms in this blast exposed sample. These findings should be interpreted with caution since the power of these analyses was limited by a small (n=16) group of non mTBI participants. The very small effect size for the PCL (d=0.18) does suggest that even if significance were achieved with a larger sample size, any relationship of mTBI diagnosis to PTSD symptom severity appears weak. When we analyzed only participants without PTSD (n=88), power was limited even further; but there was again no significant difference in PCL scores between mTBI diagnosis groups (d=0.17). Regarding PCS symptoms, the small non-TBI group size has less bearing on results interpretation because persons diagnosed with mTBI had virtually identical mean RPQ scores as those without mTBI diagnosis with effect sizes that were either unmeasurable or < 0.02.

Much has been speculated about comborbid PTSD and mTBI regarding whether one increases risk or impedes recovery of the other. Our findings do not support the hypothesis that a recent history of blast-related mTBI is a significant risk factor for PTSD or that mTBI significantly exacerbates or ameliorates PTSD symptom severity. In contrast, our data does support the hypothesis that PTSD influences PCS symptom severity because those with PTSD had higher RPQ scores than those without PTSD. Despite the small sample size, this finding was a trend ($p=0.09$) under strict DSM-IV criteria and reached significance ($p=0.003$) under the relaxed criteria. Because similar findings have been reported by others including Hoge et al (13), this underscores the importance of considering the influence of PTSD in studies of mTBI outcome in blast-exposed samples.

The lack of association found between blast-related mTBI and residual PTSD or PCS symptoms is perhaps unsurprising in view of the divisive existing literature. Findings similar to ours have been reported in several investigations (32-34), while others have shown the opposite, that historical blast-related mTBI is associated with both PCS and PTSD symptom severity (15, 35). Differences in methodology among these studies, including differing operational definitions of mTBI, makes the conflicting evidence difficult to reconcile. In exploratory analyses of the PTSD negative sub-group, we did find a trend toward higher PCS scores among those with more than one blast exposure. This may reflect sub-clinical, or so called sub-concussive, insults to the brain from multiple blast exposures or it may simply indicate a higher degree of post-deployment psychologically induced stress short of clinical PTSD as suggested by their higher PCL scores. Regardless, it appears further research is still needed to better elucidate what if any link exists between blast-related mTBI and chronic PCS or PTSD symptoms.

Regarding the diagnostic accuracy of the PCL, our results indicate that the total score method performed better than the SCM across a wide range of cut scores for both relaxed and strict criteria. Overall, the diagnostic accuracy of the PCL under either set of criteria was in the range of “moderate”

agreement (36) across the cut scores with higher *kappa* values and is similar to previous studies of the PCL (5). Which criteria were applied to the MINI affected the specific accuracy parameter values at given cut scores and therefore cut score selection was criteria dependent. The choice of the "best" PCL cut score in any population is complex and depends on which specific accuracy index(s) a researcher desires to maximize. A balanced approach values nearness of calculated prevalence to true prevalence, higher correct classification rate, and higher *kappa* statistic. However, the most accurate calculated prevalence, the peak classification rate, and the peak *kappa* typically do not occur at the same cut score. Moreover, because of sampling error there is usually a range of cut scores for which the best values (true prevalence, peak *kappa*, and peak classification rate) are all contained within their respective 95% C.I. In our data, under strict criteria (requiring A2) the true prevalence was 16%, the peak *kappa* value was 0.49, the peak classification rate 87%, and each occurred at different cut scores. The range of cut scores was 61.5 – 67.5 for which all three values (16%, 0.49, 87%) resided within their respective parameter's 95% C.I. But for practical implementation a single cut point is desired, so we made the qualitative choice to give precedence to the *kappa* statistic. Within the 61.5 – 67.5 range, the peak *kappa* value of 0.49 was found at the cut score of 66. This specific cut-point and range are much higher than convention and higher than the cut-point of 60 found in the recent carefully done study on the psychometric properties of the PCL by Keen et al on a sample of 100% male Veterans (37). Our higher cut-point compared to Keen et al may reflect a greater prevalence of combat experience, (100% versus 65%) and/or a shorter time from exposure (mean age 26.0 +/- 7.2 versus 47.4 +/- 7.1). The prevalence of mTBI also may have differed but was not reported by Keen.

Similarly, under relaxed criteria (aligning with DSM-V by ignoring A2), the true prevalence was 26.4%, the peak kappa was 0.54, and the peak classification rate was 81%. The range of cut scores was 54.5 – 62.5 where these values fell within their respective 95% C.I. Within this range, the peak kappa

value occurred at a cut score of 58. Since our "relaxed" criteria approximates DSM-V by also removing the A2 criterion, it is reasonable to opine that this cut-point of 58 is better for extrapolating from legacy DSM-IV PCL data into DSM-V. For future prospective PCL research, PTSD symptom data will likely be collected with the just developed DSM-V version of the PCL, coined the PCL-5 (http://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp). The PCL-5 not only adds the three additional DSM-V symptom items but also rescales the Likert ranges for each item from 1-5 to 0-4. If one were to assume that the mean score of the three additional items is equal to the mean score of the other 17 items, then the PCL-5 equivalent cut-point could easily be estimated from the legacy PCL [(legacy PCL total ÷ 17 – 1) x 20 = PCL-5 total]. Under this assumption, our found cut-point of 58 for the legacy PCL would translate into a PCL-5 rounded cut-point of 48.

As noted earlier, the decision regarding what PCL cut score is "best" depends on the context of the evaluation and which accuracy parameter(s) are desired to be maximized. As a clinical screening to indicate potential need for future evaluation and treatment, more weight should be placed on maximizing sensitivity, so a lower cut-point is preferred. In this scenario, the identified cut score of 58 (employing the relaxed PTSD criteria) will have poor utility, as 29% of those with PTSD in our sample will be missed. A lower cut score will reduce false negatives, but will also lead to increased false positives and reduced efficiency. For example, all participants with a MINI diagnosis of PTSD had a PCL score of greater than 38.5. Thus, 100% of those scoring above that cut score would be detected. However, 67% of those screening positive would be false positives, potentially overwhelming clinical resources available for second-level PTSD assessments. The appropriate cut-point threshold employed as part of a clinical screening program (38) is a decision that must weigh resources, available treatments, ethical considerations, stakeholder acceptability, and other important factors.

When the PCL is used to detect only those with a high likelihood of PTSD, a clinical researcher may prefer a higher cut score to minimize false positives (i.e., maximize PPP) and reduce the costs of clinical interviews needed to confirm diagnosis. The cut score one chooses will depend on the relative cost of screening to the second-level interview evaluations, the size of the population available for screening, and the desired number of study enrollees. Similarly, when using existent PCL data to group persons into probable vs. unlikely PTSD diagnosis on strict DSM-IV criteria for research purposes, the threshold for misdiagnosis and uncertainty will depend on a study's objective. Investigators are encouraged to consult the literature and consider the potential benefits and pitfalls of using the PCL as an indicator of probable PTSD when developing new research. We have provided data on the diagnostic accuracy parameters across the entire spectrum of cut-points to enable choosing the parameter weightings that best fit the specific purpose. The specific qualitatively "best" cut-points that we identified may be useful as clinical research thresholds because we balanced parameters such that the vast majority of those classified as positive and negative will be true positives and true negatives respectively.

Although this study's diagnostic accuracy results support the utility of the PCL as a screening tool for probable PTSD for blast-exposed individuals, they may not generalize to the post-deployment population at large in which there are widely varying deployment time periods, geographic locations, and duty assignments. Our findings are more likely to generalize to populations that have a similarly elevated risk of TBI and PCS such as Veterans and SMs with positive initial TBI screens and are a similar time-frame post-deployment. Our sample had demographic characteristics similar to other reports on PTSD from the blast exposed OIF/OEF/OND population (Kontos et al (15), 96% males and mean age of 29.5 +/– 6.8 years; Adler et al,(29) 98% male; 48% married, 45% single, 7% divorced. Like these studies, ours may not generalize to females. Also noteworthy is that we did not include moderate-

severe TBI in whom it is generally accepted are more protected from PTSD given longer periods of retrograde and anterograde amnesia.

One weakness of this study is sample size which resulted in fairly large 95% confidence intervals for diagnostic accuracy parameters. Confidence intervals and effect sizes where relevant are provided to assist the reader in making their own interpretation. The nature of the sample offers both strengths and weakness. It fills an important research gap in that there is sparse empirical data on diagnostic accuracy of the PCL in military blast exposed populations at high risk for PTSD and TBI. Conversely, the results may not generalize to non-combat stressful event exposures and may not generalize to post-deployment SMs and Veterans without blast exposure. Additionally we enrolled participants from a narrow geographical region and the characteristics of blast exposure may differ from those who returned post-deployment to other regions. The sample was almost entirely male, so results may not generalize to females. Another potential weakness is by using the DSM-IV based MINI and PCL available at the time of study implementation; we could only approximate the future adoption of the DSM-V criteria by removing the A2 criteria. But this study's findings should remain useful to researchers and others given the plethora of research and administrative data both historical and still being collected using the existing DSM-IV version of the PCL.

Conclusion:

Among these blast-exposed SMs and Veterans, the prevalence rate for PTSD using DSM-IV criteria depended on whether the A2 criterion was included; the immediate subjective response to a traumatic event consisting of "intense fear, helplessness, or horror". The prevalence was higher when using the DSM-V like relaxed criteria compared to strictly adhering to DSM-IV and enforcing A2. PTSD prevalence rates did not differ between participants with and without blast-related mTBI under either set of criteria. Regarding symptoms, participants with PTSD had not only higher PCL scores, but

also higher RPQ scores than those without PTSD. Participants with mTBI were indistinguishable from those without TBI on symptom scores although power was limited by the small non-TBI group size. Regarding diagnostic accuracy of the PCL, the total score method performed better than the SCM. Using a balanced approach among the accuracy parameters and their 95% CI, the best cut score range was 61.5 – 67.5 under strict criteria and 54.5 – 62.5 under relaxed criteria. Within this range, the peak *kappa* value was at cut scores of 66 and 58 respectively. These finding should be useful for studies in this population that rely on the legacy DSM-IV derived PCL instrument to categorize persons by way of PTSD diagnosis.

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Table 1: Demographic Characteristics of Sample (n = 106)

Variable	Median	IQR
Age at baseline, years	23.0	22.0 to 27.0

Variable	Count	Percent
Sex		
Male	105	99.0
Female	1	1.0
mTBI prior to military service		
Yes	34	34.2
No	71	65.8
Military Blast Experiences		
One	24	22.9
2-5	48	45.7
>5	32	30.5
mTBI during worst experience		
Yes	90	84.9
No	16	15.1
Marital Status		
Married	48	45.7
Divorced	6	5.7
Single	51	48.6
Race		
Caucasian	87	82.9
African American	9	8.6
Other	9	8.6
Ethnicity		
Hispanic	15	14.3
Non-Hispanic	90	85.7
Highest Level of Education		
< High School Graduate	2	1.9
High School Graduate	61	58.1

Some College	32	30.5
College Graduate	10	9.5
Prior Deployment Military Status		
Active Duty	93	88.6
Selective Reserves – National Guard	5	4.8
Selective Reserves – Reserve	5	4.8
Other	2	1.9

IQR = interquartile range

Table 2. Frequencies of most psychologically traumatic event types

Classification	Type of Event	N	%
Combat Event			86.8
	witnessed the serious injury or death of someone from my unit, an ally unit, or other friendly personnel	58	
	experienced an improvised explosive device (IED) that was detonated	28	
	experienced incoming small arms fire, artillery, rockets, mortars, or bombs from enemy troops (or friendly fire)	8	
	went on a combat patrol, convoy, or other mission that provided risk of death	4	
	observed seriously injured or dead bodies	3	
	Other	4	
Non-Combat Event			13.2
	sudden and unexpected death of a close friend or loved one	10	
	a natural disaster (such as a hurricane or earthquake)	2	
	Other	3	

Table 3. PTSD and PCS symptom severity by PTSD groups under Strict DSM-IV criteria

Strict DSM-IV criteria	Frequency	Percent	Mean PCL (sd)	Mean RPQ (sd)
PTSD positive	17	16.0	62.4 (11.0)*	35.5(11.2)
PTSD negative	89	84.0	45.9 (13.0)*	30.5 (10.7)

Symbol* denotes significantly different at $p < 0.05$ level.

Table 4. PTSD and PCS symptom severity by PTSD groups under Relaxed DSM-IV criteria

Relaxed DSM-IV criteria	Frequency	Percent	Mean PCL (sd)	Mean RPQ (sd)
PTSD positive	28	26.4	61.0 (11.6)*	36.4 (11.2)^
PTSD negative	78	73.6	44.0 (12.0)*	29.5 (10.2)^

Symbols * and ^ denote significantly different at $p < 0.05$ level

Table 5. Diagnostic Accuracy of the PCL Using "Strict" PTSD Criteria at a PTSD Prevalence of 16.0%.

	Sensitivity	Specificity	PPP	NPP	Classification	Kappa	Estimated Prevalence
SCM	.88 (.80-.93)	.56 (.47-.65)	.28 (.20-.37)	.96 (.90-.99)	.61 (.52-.70)	.23 (.16-.32)	51% (42%-60%)
Cut Score							
38.5	1.0 (.96-1.0)	.25 (.17-.34)	.20 (.14-.29)	1.0 (.96-1.0)	.37 (.28-.46)	.10 (.05-.17)	79% (71%-86%)
39.5	.94 (.88-.97)	.30 (.22-.40)	.21 (.14-.29)	.96 (.91-.99)	.41 (.32-.50)	.10 (.05-.17)	74% (64%-81%)
40.5	.94 (.88-.97)	.38 (.30-.48)	.23 (.16-.31)	.97 (.92-.99)	.47 (.38-.57)	.14 (.09-.22)	67% (58%-75%)
41.5	.94 (.88-.97)	.43 (.34-.52)	.24 (.17-.33)	.97 (.92-1.0)	.51 (.42-.60)	.17 (.11-.25)	63% (54%-72%)
42.5	.88 (.81-.93)	.47 (.38-.57)	.24 (.17-.33)	.95 (.89-.98)	.54 (.44-.63)	.17 (.11-.25)	58% (49%-67%)
44.0	.88 (.81-.93)	.51 (.41-.60)	.25 (.18-.35)	.96 (.90-.99)	.57 (.47-.66)	.19 (.13-.28)	56% (46%-65%)
45.5	.88 (.81-.93)	.54 (.44-.63)	.27 (.19-.36)	.96 (.90-.99)	.59 (.50-.68)	.22 (.15-.31)	53% (43%-62%)
46.5	.88 (.81-.93)	.57 (.48-.66)	.28 (.21-.38)	.96 (.90-.99)	.62 (.53-.71)	.25 (.17-.34)	50% (41%-59%)
47.5	.88 (.81-.93)	.58 (.49-.67)	.29 (.21-.38)	.96 (.90-.99)	.63 (.54-.72)	.25 (.18-.35)	49% (40%-58%)
48.5	.88 (.81-.93)	.65 (.56-.74)	.33 (.24-.42)	.97 (.91-.99)	.69 (.59-.77)	.32 (.24-.41)	43% (34%-53%)
49.5	.88 (.81-.93)	.66 (.57-.75)	.33 (.25-.43)	.97 (.91-.99)	.70 (.60-.78)	.33 (.25-.42)	42% (33%-52%)
50.5	.88 (.81-.93)	.69 (.59-.77)	.35 (.26-.44)	.97 (.91-.99)	.72 (.62-.79)	.35 (.27-.45)	41% (32%-50%)
51.5	.88 (.81-.93)	.70 (.60-.78)	.36 (.27-.45)	.97 (.91-.99)	.73 (.63-.80)	.36 (.28-.46)	40% (31%-49%)
52.5	.82 (.74-.89)	.73 (.64-.81)	.37 (.28-.46)	.96 (.90-.98)	.75 (.65-.82)	.37 (.28-.46)	36% (27%-45%)
54.5	.76 (.68-.84)	.74 (.65-.82)	.36 (.28-.46)	.94 (.88-.98)	.75 (.65-.82)	.35 (.26-.44)	34% (26%-43%)
56.5	.76 (.68-.84)	.75 (.66-.83)	.37 (.29-.47)	.94 (.88-.98)	.75 (.66-.83)	.36 (.28-.46)	33% (25%-42%)
58.0	.71 (.61-.78)	.78 (.69-.84)	.38 (.29-.47)	.93 (.87-.97)	.76 (.67-.84)	.35 (.27-.45)	30% (22%-40%)
59.5	.65 (.55-.73)	.79 (.70-.85)	.37 (.28-.46)	.92 (.85-.96)	.76 (.67-.84)	.33 (.25-.43)	28% (21%-38%)
60.5	.59 (.49-.68)	.82 (.74-.88)	.38 (.30-.48)	.91 (.84-.95)	.78 (.69-.85)	.34 (.25-.43)	25% (17%-34%)
61.5	.59 (.49-.68)	.87 (.79-.92)	.45 (.36-.55)	.92 (.85-.96)	.82 (.74-.88)	.41 (.32-.50)	21% (14%-29%)
62.5	.59 (.49-.68)	.88 (.80-.93)	.48 (.38-.57)	.92 (.85-.96)	.83 (.75-.89)	.42 (.33-.52)	20% (13%-28%)
63.5	.53 (.44-.62)	.90 (.83-.94)	.50 (.41-.59)	.91 (.84-.95)	.84 (.76-.90)	.42 (.33-.51)	17% (11%-25%)
64.5	.53 (.44-.62)	.92 (.85-.96)	.56 (.47-.65)	.91 (.84-.95)	.86 (.78-.91)	.46 (.37-.56)	15% (09%-23%)
66.0	.53 (.44-.62)	.93 (.87-.97)	.60 (.50-.69)	.91 (.84-.95)	.87 (.79-.92)	.49 (.39-.58)	14% (09%-22%)
67.5	.41 (.32-.51)	.94 (.88-.98)	.58 (.49-.67)	.89 (.82-.94)	.86 (.78-.91)	.40 (.32-.50)	11% (06%-19%)
68.5	.29 (.22-.39)	.94 (.88-.98)	.50 (.41-.59)	.88 (.80-.93)	.84 (.76-.90)	.29 (.21-.38)	09% (05%-17%)
70.0	.24 (.16-.32)	.96 (.89-.98)	.50 (.41-.59)	.87 (.79-.92)	.84 (.76-.90)	.24 (.17-.33)	08% (04%-14%)
72.0	.24 (.16-.32)	.98 (.92-1.0)	.67 (.57-.75)	.87 (.79-.92)	.86 (.78-.91)	.29 (.21-.38)	06% (02%-12%)
73.5	.12 (.07-.19)	.98 (.92-1.0)	.50 (.41-.59)	.85 (.77-.91)	.84 (.76-.90)	.14 (.08-.22)	04% (01%-10%)
74.5	.06 (.03-.12)	.98 (.92-1.0)	.33 (.25-.43)	.84 (.76-.90)	.83 (.75-.89)	.05 (.02-.12)	03% (01%-08%)
76.0	.06 (.03-.12)	.99 (.94-1.0)	.50 (.41-.59)	.85 (.76-.90)	.84 (.76-.90)	.07 (.04-.14)	02% (00%-07%)

Notes. PPP = positive predictive power, NPP = negative predictive power, LR = likelihood ratio, SCM = symptom cluster method. Ranges in parentheses indicate 95% Wald confidence intervals.

Table 6. Diagnostic Accuracy of the PCL Using "Relaxed" PTSD Criteria at a PTSD Prevalence of 26.4%.

	Sensitivity	Specificity	PPP	NPP	Classification	Kappa	Estimated Prevalence
SCM	.86 (.78-.91)	.61 (.51-.70)	.45 (.35-.54)	.92 (.85-.96)	.68 (.58-.76)	.36 (.28-.46)	52% (42%-61%)
Cut Score							
38.5	1.0 (.96-1.0)	.28 (.20-.37)	.33 (.25-.43)	1.0 (.96-1.0)	.47 (.38-.57)	.17 (.11-.26)	79% (71%-86%)
39.5	.93 (.86-.97)	.33 (.25-.43)	.33 (.25-.43)	.93 (.86-.97)	.49 (.40-.58)	.17 (.11-.25)	74% (64%-81%)
40.5	.89 (.82-.94)	.41 (.32-.51)	.35 (.27-.45)	.91 (.84-.96)	.54 (.44-.63)	.20 (.14-.29)	67% (58%-75%)
41.5	.89 (.82-.94)	.46 (.37-.56)	.37 (.29-.47)	.92 (.85-.96)	.58 (.48-.67)	.25 (.17-.34)	63% (54%-72%)
42.5	.86 (.78-.91)	.51 (.42-.61)	.39 (.30-.48)	.91 (.84-.95)	.60 (.51-.69)	.27 (.19-.36)	58% (49%-67%)
44.0	.86 (.78-.91)	.55 (.46-.64)	.41 (.32-.50)	.91 (.84-.96)	.63 (.54-.72)	.30 (.22-.39)	56% (46%-65%)
45.5	.86 (.78-.91)	.59 (.49-.68)	.43 (.34-.52)	.92 (.85-.96)	.66 (.57-.74)	.34 (.26-.43)	53% (43%-62%)
46.5	.82 (.74-.88)	.62 (.52-.70)	.43 (.34-.53)	.91 (.83-.95)	.67 (.58-.75)	.34 (.26-.43)	50% (41%-59%)
47.5	.82 (.74-.88)	.63 (.53-.71)	.44 (.35-.54)	.91 (.84-.95)	.68 (.59-.76)	.35 (.27-.45)	49% (40%-58%)
48.5	.82 (.74-.88)	.71 (.61-.78)	.50 (.41-.59)	.92 (.85-.96)	.74 (.64-.81)	.44 (.35-.53)	43% (34%-53%)
49.5	.82 (.74-.88)	.72 (.63-.80)	.51 (.42-.60)	.92 (.85-.96)	.75 (.65-.82)	.45 (.36-.55)	42% (33%-52%)
50.5	.82 (.74-.88)	.74 (.65-.82)	.53 (.44-.63)	.92 (.85-.96)	.76 (.67-.84)	.48 (.39-.58)	41% (32%-50%)
51.5	.82 (.74-.88)	.76 (.67-.83)	.55 (.45-.64)	.92 (.85-.96)	.77 (.68-.84)	.50 (.40-.59)	40% (31%-49%)
52.5	.79 (.70-.85)	.79 (.71-.86)	.58 (.48-.67)	.91 (.84-.95)	.79 (.71-.86)	.52 (.43-.61)	36% (27%-45%)
54.5	.75 (.66-.82)	.81 (.72-.87)	.58 (.49-.67)	.90 (.83-.95)	.79 (.71-.86)	.51 (.42-.60)	34% (26%-43%)
56.5	.75 (.66-.82)	.82 (.74-.88)	.60 (.50-.69)	.90 (.83-.95)	.80 (.72-.87)	.53 (.43-.62)	33% (25%-42%)
58.0	.71 (.62-.79)	.85 (.76-.90)	.63 (.53-.71)	.89 (.82-.94)	.81 (.73-.88)	.54 (.44-.63)	30% (22%-40%)
59.5	.68 (.58-.76)	.86 (.78-.91)	.63 (.54-.72)	.88 (.80-.93)	.81 (.73-.88)	.53 (.43-.62)	28% (21%-38%)
60.5	.54 (.44-.63)	.86 (.78-.91)	.58 (.48-.67)	.84 (.75-.90)	.77 (.68-.84)	.40 (.32-.50)	25% (17%-34%)
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66.0	.43 (.34-.52)	.96 (.90-.99)	.80 (.71-.87)	.82 (.74-.89)	.82 (.74-.88)	.46 (.37-.55)	14% (09%-22%)
67.5	.32 (.24-.42)	.96 (.90-.99)	.75 (.66-.82)	.80 (.71-.86)	.79 (.71-.86)	.35 (.26-.44)	11% (06%-19%)
68.5	.25 (.18-.34)	.96 (.90-.99)	.70 (.61-.78)	.78 (.69-.85)	.77 (.68-.84)	.27 (.19-.36)	09% (05%-17%)
70.0	.21 (.15-.30)	.97 (.92-1.0)	.75 (.66-.82)	.78 (.69-.85)	.77 (.68-.84)	.24 (.17-.33)	08% (04%-14%)
72.0	.21 (.15-.30)	1.0 (.96-1.0)	1.0 (.96-1.0)	.78 (.69-.85)	.79 (.71-.86)	.29 (.21-.38)	06% (02%-12%)

Notes. PPP = positive predictive power, NPP = negative predictive power, LR = likelihood ratio, SCM = symptom cluster method. Ranges in parentheses indicate 95% Wald confidence intervals.

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Structured interview for Mild Traumatic Brain Injury after military blast: interrater agreement and development of diagnostic algorithm

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ABSTRACT

The existing gold standard for diagnosing a suspected prior mild Traumatic Brain Injury (mTBI) is clinical interview. But it is prone to bias, especially for parsing the physical versus psychological effects of traumatic combat events, and its interrater reliability is unknown. Several standardized TBI interview instruments have been developed for research use but have similar limitations. Therefore, we developed the VCU retrospective concussion diagnostic interview, blast version (VCU rCDI-B) and undertook this cross-sectional study aiming to: 1) measure agreement among clinicians' mTBI diagnosis ratings, 2) using clinician consensus develop a fully structured diagnostic algorithm, and 3) assess accuracy of this algorithm in a separate sample. Two samples (n=66, n=37) of individuals within two years of experiencing blast effects during military deployment underwent semi-structured interview regarding their worst blast experience. Five highly trained TBI physicians independently reviewed and interpreted the interview content and gave blinded ratings of whether or not the experience was probably an mTBI. Paired interrater reliability was extremely variable with kappa ranging 0.194-0.825. In Sample-1, the physician consensus prevalence of probable mTBI was 84%. Using these diagnosis ratings, an algorithm was developed and refined from the fully structured portion of the VCU rCDI-B. The final algorithm considered certain symptom patterns more specific for mTBI than others. For example, an isolated symptom of "saw stars" was deemed sufficient to indicate mTBI whereas an isolated symptom of "dazed" ~~or "confused"~~ was not. The accuracy of this algorithm when applied against the actual physician consensus in Sample-2 was almost perfect (correctly classified = 97%, Cohen's kappa=0.91). In conclusion, we found that highly trained clinicians often disagree on historical blast-related mTBI determinations. A fully structured interview algorithm was developed from their consensus diagnosis that may serve to

enhance diagnostic standardization for clinical research in this population.

INTRODUCTION

Exposure to traumatic events is an inherent aspect of military combat. In Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND), U.S. Service Members (SMs) have experienced an especially high rate of traumatic events caused by blast. Heavily used by the insurgents, explosive munitions have accounted for about 78% of wounded in action cases, the highest proportion for any large scale conflict.[1] The effects of these frequent blast exposures include traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), both of which are considered "signature wounds" of OEF/OIF/OND. Among SMs and Veterans who were deployed, 19% are estimated to have sustained a TBI,[2] and up to 31% may have PTSD.[3] Because of the potential debilitating effects of TBI[4], both the Department of Veterans Affairs (VA) and the Department of Defense (DoD) have made early identification of, accurate diagnosis of, and access to effective treatments for TBI a research priority.

Mild TBI (mTBI) or concussion is by far the most common category of TBI during OEF/OIF/OND deployment, accounting for over 80% of cases.[5] Although mild in nomenclature, up to 20% of those sustaining an mTBI will develop Post-Concussion Syndrome (PCS), a condition of chronic symptoms that may include cognitive impairments and detrimental effects on psychosocial functioning.[6,7] And in contrast to more severe TBI, mTBI is uniquely problematic in diagnosing. The diagnosis of any severity of TBI centers on identifying ~~the effects of diffuse axonal injury (DAI), which are clinically expressed by~~ an initial period of alteration of consciousness (AOC) with or without frank loss of consciousness (LOC).[8] Various pathophysiologic processes are hypothesized to be responsible for TBI induced AOC including diffuse axonal injury (DAI).[9] With mTBI the initial AOC period can be minutes or less and

usually does not include LOC; so its determination is complex compared to severe TBI where amnesia lasts over one week and often includes an initial LOC period. The briefer its duration the more challenging it becomes to distinguish it from absence of AOC. Once the brief AOC period resolves, the diagnosis of mTBI may easily be missed as shown by a recent study of emergency department patients where less than half of those who sustained mTBI by study criteria actually received a documented diagnosis.[10] Furthermore, imaging may provide confirmatory evidence in moderate-to-severe TBI, but by definition conventional computerized tomography is normal in mTBI.[8]

Varying diagnostic criteria for mTBI exist, including the VA/DoD Common Definition of mTBI (http://www.cdc.gov/nchs/data/icd/Sep08TBI.pdf) adopted from The Centers for Disease Control and Prevention (CDC) mTBI Work Group.[11] Common among all published criteria~~,~~ are the types of information needed for diagnosis which are 1) evidence of an external physical force being applied to the head and 2) evidence of~~only the~~ immediate AOC ~~symptoms~~ signs or focal neurologic signs~~or immediate AOC signs such as seizure are used to derive the mTBI diagnosis~~.[8] Other post-injury symptoms potentially attributable to TBI (e.g., headache, dizziness, irritability, fatigue, or poor concentration) ~~that may be attributable to TBI~~ may support diagnosis and do carry prognostic significance,[12]~~can be used to support,~~ but absent evidence of AOC cannot by themselves be used to make~~,~~ a diagnosis of mTBI in adults.[11] Additionally, available guidelines do not specify what exact symptom(s) or symptom pattern(s) constitute evidence of AOC ~~"~~attributable~~"~~ to head injury and thus the determination remains open to clinician interpretation.

As an additional confounder, traumatic events such as battlefield blast exposure may result in a perception of AOC strictly on the basis of an acute stress response.[13] Shock, fear, horror, or adrenaline surge may cloud the sensorium or even lead to repressed memory. There

are no reliable means to differentiate between symptoms involving impaired awareness that are caused by severe stress versus mTBI, so differential diagnosis is problematic.[14] This problem may be heightened over time, because during recall of trauma reactions, people with severe psychological disturbance overestimate the symptoms that they had in the acute phase.[13] The residual effects of the psychological versus physical brain trauma also cannot be easily distinguished as PTSD and PCS both lack objective neurologic findings and exhibit non-specific and overlapping symptoms.[15] They may also coexist as demonstrated by one study showing that 40% of U.S. military personnel reported acute PTSD symptoms following an mTBI,[16] and another that 42% of OEF/OIF Veterans with a history of mTBI reported persistent PTSD symptoms.[17] Because of these issues, some have suggested that the more objective construct of PTA is preferred over softer symptoms of AOC such as "dazed" in diagnosing suspected combat mTBI,[13] but this approach alone would fail to identify the substantial numbers of mTBI without PTA.

The inherent challenges of combat mTBI detection have prompted extensive research efforts in the quest of more objective diagnostics. These efforts have centered on biomarker and imaging substrates of TBI, with less attention placed on refinement of the gold standard clinical assessment. While validated, structured symptom measures and mental status examinations exist to assist diagnosis in acute settings, such as athletic sidelines,[18] there is usually a time lag before formal acute medical evaluation. The examiner must determine the existence or non-existence of an initial TBI-based AOC period solely from the patient's self-reported symptom experience recall. Notwithstanding current symptoms, the interviewer must instead ascertain that a period of AOC occurred immediately after experiencing the earlier injury force.

Given these difficulties, the scientific literature lacks standard sample selection criteria for the combat mTBI population. Most studies have relied on self-classified concussion or screening instruments, such as those mentioned by Hoge and colleagues[16], or unstructured post-acute clinical evaluations; none of which have proven diagnostic accuracy for mTBI. Screening instruments of any type cannot be relied upon without additional diagnostic steps on positive screens. For example it has been shown that patients often report illogical or even frankly contradictory responses to AOC items on TBI screening questionnaires such as endorsing LOC but denying a memory gap.[19] Unstructured interviews, which could potentially vet these types of responses, are limited by the degree of examiner thoroughness, experience, expertise, and bias in question formatting and response interpretation. In research settings, using unstructured interview to diagnose mTBI has the further problems of poor transparency and questionable inter-rater reliability. It may be due to these methodologic limitations that published studies to date have been unable to disentangle all the potential risk factors and infer a major causative role of mTBI in PCS among Veterans and military SMs.

The standardization and transparency of mTBI diagnostics for research could be advanced by implementing a valid, structured interview. Formal structured interviews have been developed, validated, and used extensively in other conditions, such as those in the mental health arena, where they are considered the gold standard for diagnostic accuracy and against which shorter self-administered questionnaires are typically assessed psychometrically.[20-22] The structured interview tools developed to date for post-acute TBI diagnosis have significant short comings when applied for mTBI whether from blast or other causes. The Ohio State University TBI Identification Method (OSU TBI-ID) is the most widely used structured interview designed for retrospective identification of TBI.[23] However, sound interrater reliability has only been

reported when the case definition of TBI was "knocked out or unconscious", probably because the other AOC symptoms are less specific for TBI. This lack of proven reliability for TBI without LOC is an important limitation concerning use of the OSU TBI-ID for diagnosing mTBI because available prospective data in athletic populations shows that 80% or more of mTBI cases do not have LOC.[24,25]

Other retrospective TBI interview instruments have been developed and reported. The Boston Assessment of TBI Lifetime (BAT-L)[26] is a semi-structured interview developed for administration by a doctoral level neuropsychologist. The BAT-L is described as a "preliminary screen" using a forensic approach with open ended questions as previously described by Vanderploeg et al,[27] with open ended questioning. The Brief Traumatic Brain Injury Screen (BTBIS) is a self-report tool for "probable" TBI and problems and symptoms that may be associated with TBI.[28] This interview consists of a series of primarily open-ended questions with vetting of responses left to judgment of the interviewer, either a Masters' level psychologist or trained staff member. The Traumatic Brain Injury Questionnaire (TBIQ) is a semi-structured interview with 12 closed-ended (Y/N) response items assessing for a possible TBI incident, followed by an open-ended interview of the incident(s) identified.[29] Donnelly et al[30] described a semi-structured interview for TBI diagnosis against which the Veterans Affairs TBI Screening Tool was assessed for diagnostic accuracy, but did not report on psychometric properties of the interview instrument. These semistructured instruments are not only generally lacking published reliability data, but as with the OSU-TBI ID sensitivity and specificity has not been measured against a meaningful gold standard diagnosis such as an antecedent thorough acute clinical assessment.

In summary, the retrospective diagnosis of mTBI is challenging, especially for battlefield blast where its effects are difficult to separate from that of acute stress reaction. Unstructured clinical interview is the existing gold standard but it is susceptible to bias and has no published inter-rater reliability data, which limits its use for research. Existing interview and questionnaire tools for detecting mTBI are generally only semi-structured so do not totally eliminate potential bias and are of unproven diagnostic accuracy. Therefore, we sought to examine interrater reliability of clinicians' mTBI diagnoses made using identical interviewee blast experience information gathered during semi-structured interview. The interview tool, the VCU retrospective Concussion Diagnostic Interview-blast version (VCU rCDI-B), was developed as part of an overarching epidemiologic study of military blast exposures. The second and more central aim was to develop an automated interpretive algorithm to pair with the fully-structured component of the interview to create a highly standardized and transparent tool for retrospective diagnosis of blast-related mTBI. In order to achieve this, we separated the sample into a initial algorithm development sample and a second smaller sample to test its accuracy against a physician consensus diagnosis.

MATERIALS AND METHODS

Participants

Participants for the overarching ongoing epidemiological study were recruited via letters, advertisements, and from ambulatory health care clinics at the Hunter Holmes McGuire VA Medical Center (VAMC) Polytrauma Rehabilitation Center in Richmond, VA and at several nearby large military bases (Fort Lee Army Base in Prince George County, VA; Marine Corps Base (MCB) Camp Lejeune in Onslow County, NC; and MCB Quantico in Prince William

County, VA). Inclusion criteria were SM or Veteran with one or more blast experiences within the past two years while deployed in OIF/OEF. Since the intended population was those at high risk for physical effects of blast, "blast experience" was defined as reporting any of the following symptoms or effects during or shortly after exposure to blast or explosion: feeling dazed, confused, seeing stars, headaches, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, being struck by debris, knocked over or down, knocked into or against something, having one's helmet damaged, or being medically evacuated. Severe and Moderate TBI were the only exclusion criteria and were defined as: More than 30 minutes in coma, brain bleeding or blood clot (abnormal brain CT scan), or none of first 24 or more hours after event can be remembered (PTA > 24 hours). The current study contained two separate samples that were both derived from the overarching study sample. Sample-1, intended to develop the VCU rCDI-B diagnostic algorithm, consisted of the first 66 consecutively consented and enrolled participants who completed baseline study procedures after our semi-structured interview was added to the protocol. Sample-2, intended to cross validate the algorithm, consisted of the 37 subsequent subjects completing baseline.

Procedure:

Blast Experience Interview

After identifying their self-determined worst (or only) blast experience, each participant was administered the interview (VCU-rCDI-B) by a research coordinator. The VCU-rCDI-B is a combination of open-ended and fully structured interview developed by the one of the researchers (WCW) in order to provide an in depth assessment of a subject's blast experience and the variables that formulate the AOC construct used to diagnose mTBI. Because the fully structured component was untested, we included the open-ended portion to provide contextual

and supplementary information that may not be captured by the structured interview alone. The interview was designed to be administered in 15-30 minutes and the structured portion probed the subject on the description of the event and experiences, the recollection of the event, the injury mechanism, consciousness, all potential symptoms that might indicate immediate AOC, and outcome of the event. The interview included a structural quality assurance check intended to minimize false negative responses to the detailed but potentially abstract questioning on amnesia. If the interviewee reports memory of the (blast) event and denies any memory gap before or after the event then the interviewee is asked to verify that they had continuous memory of the event and immediate surrounding period of time; if continuous memory is denied then the memory items are administered again before moving on with the interview. Another check intended to minimize false positives is included when LOC is endorsed asking if a witness verified it.

Interviewer training consisted of providing coordinators time to familiarize themselves with the instrument, emphasizing the need to exactly adhere to the questions, embedded scripts, and decision trees, and conducting several practices with mock patients. The unstructured portion of the interview was administered first and was followed by the fully structured portion. For the unstructured portion, the coordinator asked and wrote down the responses to the following query:

> "On the screening form, we asked you to identify your worst blast event which you described as.... Today, I would like you to tell me in as much detail as possible what happened to you and what you felt." [*Interviewer instructions: Make sure to get a clear narrative about events leading up to the blast, information about the blast event, and information about what happened after the blast including what he/she experienced physically and emotionally*].

The entire VCU rCDI-B is provided in Appendix A for those seeking more detail on the fully structured portion.

Primary Outcome Measures

The primary outcome measure was the five physicians' independent diagnoses of whether the participant probably did or did not sustain a mTBI during the interviewed event. All physicians were board certified or eligible in Physical Medicine and Rehabilitation and considered themselves TBI experts by virtue of training and experience. Two were investigators for the overarching study. Physicians were each separately provided with de-identified copies of the subject's VCU-rCDI-B responses and were instructed to use their best clinical judgment to determine the diagnosis based on the aforementioned CDC definition of mTBI. In cases of diagnostic uncertainty, they were asked to use their best judgment to make a choice of mTBI versus no mTBI using the legal definition of probability as a reference (greater or less than 50% probability).They independently reviewed and interpreted the interview data and all were ~~each~~ blinded to any other subject information or the other physician~~'s~~ rating~~(s)~~.

Sample-1 (n=66) ratings procedure and algorithm development:

~~Physicians were instructed to provide a diagnosis rating based on their independent review and using the aforementioned CDC definition of mTBI. In cases of diagnostic uncertainty, they were asked to use their best judgment to make a choice of mTBI versus no mTBI using the legal definition of probability as a reference (greater or less than 50% probability). Because~~ In sample-1 we aimed~~desired~~ to examine interrater reliability of~~on~~ not only the~~is forced~~ yes/no TBI determination but also ~~on an~~ ordinal TBI likelihood scale ratings, so we ~~also~~ instructed the physicians~~m~~ to also rate their level of certainty on each diagnosis. Specifically, they were asked to rate their yes versus no determination as being either of high or

low certainty using 90% or higher confidence as the anchor for high certainty. Thus the following clinician rating was generated for each participant with the TBI likelihood ordinal scale ranking denoted in parentheses:

(>=2) Yes; most likely is a TBI

(3) TBI with high certainty; at least 90% confidence subject had TBI,

(2) TBI with low certainty; subject most likely had TBI but less than 90% confident,

(<=1) No; most likely is not a TBI

(1) No TBI with low certainty; subject most likely did not have TBI but less than 90% confident,

(0) No TBI with high certainty; at least 90% confidence subject did not have TBI.

For the purposes of determining the physician consensus rating ~~and subsequently for interview algorithm development~~, only the dichotomous scale of most likely yes versus most likely no was used. A consensus rating was defined as the majority physician diagnosis (3 out of 5 physicians) of this scale. That is, if >=3 of 5 physicians independently determined that a subject certainly or most likely had a mTBI, then the physician consensus rating was positive; if >= 3 of 5 ~~the~~ ratings were~~as~~ certainly not or most likely ~~did~~ not then consensus rating was defined as negative for TBI. Thus, the consensus rating for each participant was a compilation of the independent blinded individual physician interpretations and constituted the gold standard against which algorithm development described in the Results section sought to match.

Sample-2 (n=37) ratings procedure:

Interview diagnosis of mTBI after blast

A blinded physician rating protocol similar to Sample-1 was employed for Sample-2 again using five physicians; four of the five from Sample-1 and one other physician. As in Sample-1, the raters independently classified each participant as positive for mTBI using a cut-point of 50% probability of mTBI, and this dichotomous scale was used to determine the consensus rating with >= 3 physicians considered the consensus. Differing from the Sample-1, a TBI likelihood scale was not used.

Statistical Methods

The distributions of the demographic and blast experience characteristics for each sample were summarized with frequency counts and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Medians and IQRs were chosen as they are better descriptors of the center and spread of severely skewed continuous variables.

The distributions of the physician diagnoses of mTBI for each sample of subjects were examined and summarized for both the ordinal scales and the binary outcome scales (Probably mTBI, Probably Not mTBI). A simple and weighted kappa statistic was computed to assess the reliability, or agreement, between each pair of physicians on the binary and ordinal rating scales respectively. Values of kappa close to 1 indicate agreement and values close to 0 indicate random assessment. The kappa statistics were interpreted using the schematic recommended by Landis & Koch.[31] Kappa values, simple or weighted, less than 0 are considered to be indicative of no agreement, those ranging 0.00 – 0.20 indicate slight agreement, 0.21–0.40 indicates fair agreement, 0.41–0.60 indicates moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement. Fleiss-Cohen weights were used for the computation of the weighted kappa statistic and asymptotic standard errors (ASEs) and 95% confidence intervals (CIs) were computed for each statistic.

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Interview diagnosis of mTBI after blast

The final VCU-rCDI-B automated diagnostic algorithm was compared to the physician consensus in Sample-2 using the following parameters: correct classification rate, positive predictive value (PPV), negative predicted value (NPV), sensitivity and specificity. Due to these estimates being close to the upper bound, a Wilson 95% CI was reported with each of these quantities.[32]. Lastly, Cohen's simple kappa was also calculated to better understand the predictive ability of the algorithm. A test of chance agreement between the algorithm and physician consensus for each of the kappa statistics was performed at the 0.05 level.

RESULTS

Description of Sample Characteristics

The demographic, military, and blast exposure characteristics for categorical variables are summarized in Table 1 for both samples. Overall, both samples were very similar regarding their characteristics, except Sample-2 had comparatively more African-American subjects (by percentage).

Insert Table 1 about here

The median ages of the participants was 24 years old (IQR = 21 – 27) and 23 (IQR = 22 – 26) for Sample-1 and -2, respectively.Sample-1 participants were evaluated at a median of 9.1 months (IQR = 6.3 – 9.7) after their self-described worst blast experience for which they were interviewed. Nominally, Sample-2 participants had greater elapsed time with evaluation

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occurring a median of 13.2 months (IQR = 7.7 - 22.5) since their index blast experience. Sample-2 also tended to have more blast experiences, with almost half (49%) having 3 or more blast experiences, compared to only 34% for Sample-1 (Table 1). None of these qualitative differences reached statistical significance.

Distribution of Physician Diagnoses by Sample

The distributions of the physician diagnoses of mTBI are summarized separately by physician for both samples in Table 2. The 4-level multinomial outcome for Sample-1 is shown along with the binary outcome (Probably mTBI, Probably Not mTBI) for both samples. The proportion diagnosed positive for probable mTBI by each physician ranged from 58% to 93% in Sample-1 and from 59% to 86% in Sample-2. The proportion of subjects diagnosed with probable mTBI using physician consensus designation was 85% in Sample-1 and 84% in Sample-2.

Insert Table 2 about here

Inter-Rater Reliability of Physician Diagnoses

Inter-rater reliability was first assessed using the binary scales. As displayed in Table 3, Sample-1 simple kappa values for the ten physician pairs ranged from 0.314 to 0.615, and Sample-2 kappa values for the ten pairs ranged from 0.194 to 0.825.

Interview diagnosis of mTBI after blast

Insert Table 3 about here

Weighted kappa values for the likelihood of TBI scale (high certainty not, probably not, probably TBI, high certainty TBI) used in Sample-1 are shown in Table 4 with the ten pairs ranging from 0.283 to 0.641.

Insert Table 4 about here

VCU-rCDI-B Automated Algorithm development and description

The framework for the automated diagnostic algorithm ~~from the fully structured portion of the VCU-rCDI-B~~ was based on the first author's own mTBI clinical interview and decision-making method for identifying TBI induced AOC that was refined during over 20yrs of experience. Once a potential concussive event is identified this method ~~This~~ is a two step hierarchical process consisting~~ed~~ of first probing and vetting the PTA construct followed by probing and vetting other potential AOC symptoms if PTA was not already ruled in. The conceptual basis for ~~formulating and adjusting~~ the item level decision tree rules ~~for each item~~ within the algorithm was that diagnosticians would consider some symptoms and symptom combinations to be~~are~~ more specific than others for AOC caused by TBI and that some participants would give illogical or contradictory responses ~~during interview~~. In order to form the first draft set of decision tree rules we inspected the contrasting patterns of item responses for those who were physician consensus positive versus negative for mTBI. This first draft set of~~e~~ algorithm tree rules was then refined through trial and error adjustments until maximizing the

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number of correct classifications achieved vis-à-vis the consensus diagnosis. Through this process, we found that the majority of the physician group did in fact g~~a~~ive precedence to patterns of responses that showed clear evidence of PTA and less credence to illogical PTA patterns such as remembering the blast but not remembering the time before and~~or~~ after. ~~Additionally, t~~The majority also appeared to judge "dazed" as the non-PTA symptom least specific for AOC due to blast-related mTBI, especially when it was instantaneous (< 1 min) in duration. Furthermore, the majority judged each non-PTA AOC symptom (dazed, confused, saw stars) to be less specific when it was endorsed lasting over 24 hours; perhaps being viewed as non-organic symptom aggrandizement. We also found that including the "head struck" item in the algorithm provided a very slight improvement in correct classification; perhaps in questionable cases the raters were swayed by evidence that blunt head trauma accompanied the blast event. Other items in the interview such as the blast distance and directionality did not enhance the correct classification rate. The final best-fitting algorithm built from Sample ~~-~~-1 is displayed in Figure 1 and Figure 2. It generated a correct classification rate of 61/66 (92%) with 2 false positives and 3 false negatives against the actual consensus ratings.

Insert Figure 1 about here

Insert Figure 2 about here

The TBI ratings from the final diagnostic algorithm are shown in Table 5. It classified 55 (83%) subjects as positive for Probable mTBI in Sample-1 and 30 (81%) subjects in Sample-2, proportions very similar to physician consensus.

Insert Table 5 about here

Table 6 shows the performance of the diagnostic algorithm compared to the physician consensus, the proxy gold standard, within Sample-2, the cross validation sample.

Insert Table 6 about here

The VCU rCDI-B automated algorithm achieved near perfect prediction in comparison with the physician consensus, as the algorithm and consensus agreed for 97% of participants (95% CI: 86%, 100%). Cohen's kappa was 0.91 (ASE=0.09, 95% CI: 0.73, 1.00), reflecting almost perfect agreement. The other measures of agreement also reflect this near perfect prediction: sensitivity and specificity of the algorithm were 1.00 (95% CI: 0.61, 1.00) and 0.97 (95% CI: 0.84, 0.99), respectively, and the PPV and NPV were 1.00 (95% CI: 0.89, 1.00) and 0.86 (95% CI: 0.49, 0.97), respectively.

DISCUSSION

As noted earlier, published TBI interview instruments have unknown diagnostic accuracy for prior mTBI, so unstructured clinician interview remains the most widely accepted gold standard method.[33,34] Nevertheless, such freestyle mTBI interviews are susceptible to interviewer differences including bias and they lack of transparency, both of which limit interpretability when used in research. There is also a complete absence of inter-rater reliability data of unstructured mTBI interviews. VHA administrative data suggests reliability is weak given extreme inter-site variability in the proportion of positive versus negative mTBI diagnosis determinations made during comprehensive clinical evaluation of TBI screen positives (VA intranet site not accessible to public; comparable public internet site can be found at http://www.queri.research.va.gov/ptbri/utilization_reports.cfm).[35,36] Although an evaluation "template" exists, these comprehensive TBI evaluations rely on unstructured interview to determine the historical diagnosis of TBI.[33]

In the current study of physician ratings of a combined structured and unstructured interview, the range of probable mTBI diagnoses within both the samples were very wide (Sample-1 range 58 – 93%; Sample-2 range 58 – 86%). Strength of pair-wise inter-rater reliability (e.g. kappa coefficients) was highly variable, ranging all the way from minimal (k=0.19) to substantial (k=0.82). On the mTBI likelihood ordinal scale, paired agreement measures that accounted for magnitude (e.g. weighted kappa coefficients) had similarly very wide ranges (Sample-1, k=0.283-0.641). These levels of agreement involving experts with extensive training and experience in mTBI are less than ideal and echo the VHA administrative data. Although methodology limitations exist, our data suggest that individual "clinical

judgments" in determining a historical mTBI after blast are not reliable enough for research use as the proxy gold standard.

In effort to increase standardization of the mTBI interview and determination process for research purposes, we developed a fully structured, transparent and automated algorithm from our mTBI interview. The interview itself probed for all potential symptoms that might indicate immediate AOC. It also included two important quality assurance structural features; the first was intended to minimize false negative responses to the detailed but potentially abstract questioning on amnesia, and the second was intended to minimize false positives for self-reported LOC.

The final diagnostic algorithm represents the study clinicians' collective interpretation of the interview data. In essence, it provides a clinician group consensus on an operational definition of historical blast-related mTBI. The algorithm incorporates the various amnesia symptom items to check for logical consistency with PTA such that certain combinations are considered non-physiologic of mTBI (such as remembering the blast, having a retrograde memory gap, and not having an antegrade memory gap). The algorithm also weighs the relative importance of other AOC symptoms in recognition that they have differing specificity for mTBI after blast. For example the clinician raters considered the AOC symptom "dazed" as least specific for mTBI. Historically, dazed has been considered a controversial symptom for indicating TBI induced AOC to the extent that published standardized diagnostic criteria differ on its inclusion.[8] ~~Thus, i~~In ~~the~~our algorithm "dazed" must be accompanied by either "confused" or "saw stars" in order to diagnosis a blast related mTBI. Whereas a stand-alone symptom of "confused" or "saw stars" indicates a mTBI was sustained if the person also endorsed that their head was struck. The endorsement of "saw stars" is conventionally construed as a patient's

concrete portrayal of altered consciousness but the study physician(s) may have also construed it as a transient focal neurologic sign. Finally, a minimum and maximum time frame was used to define physiologic duration of AOC due to mTBI such that participants who reported 0 minutes duration or still having the symptom many months after blast were considered negative for that symptom.

The lack of sound inter-rater reliability found on the interpretation of the interview content highlights the importance of this study's development and preliminary validation of a novel fully structured interview and algorithm. The combined interview and algorithm tool may permit better diagnostic transparency and standardization for clinical research in a population where definitive diagnostics have proven elusive. The rigorous methodology to develop the algorithm included blinding of physician ratings. The structure of the interview, including no follow-up questions on the open-ended portion, served to remove all interviewer bias during symptom history probing and gathering. The results should best generalize to settings where individuals with a high probability of having sustained a prior blast-related TBI are evaluated such as VA Polytrauma clinics. The definition of a blast experience used as inclusion criteria in this study were similar to the OEF/OIF TBI screen used by the VHA, and the distribution of positive mTBI diagnoses in our study is similar to some regional administrative data from the VHA comprehensive TBI evaluations. (VA intranet site not publically accessible; comparable public internet site is found at http://www.queri.research.va.gov/ptbri/utilization_reports.cfm).

It is unknown whether these findings will generalize beyond blast-related mTBI populations. They may not be applicable to other settings of possible mTBI where there is a lower chance of psychological trauma accompanying the traumatic force. For example, the symptom of "dazed" may have greater specificity for clinician determined mTBI incurred during

athletic or recreational activities. Nevertheless, even if the pattern and combination of endorsed symptoms turns out to be different across trauma settings researchers may find it advantageous to gather information using the VCU-rCDI-B given its tight standardization. The VCU-rCDI-B can readily be adapted for blunt mechanisms of mTBI with the VCU-rCDI-B can simply substitute "____" (event) for "blast" (event). Although testing for diagnostic accuracy in a non-blast event population is recommended, we have developed the VCU-rCDI-G (general version) which can be provided upon request.

The primary advantage of using this instrument as compared to unstructured or existing semi-structured interviews will likely be in research settings, especially multi-center studies where a high degree of standardization is crucial. Even if future research indicates the operational definition of blast-related mTBI later should differ from our clinician consensus, collecting the data with this tool will facilitate data reanalysis using that more valid definition. For example if it is later determined that the "saw stars" is 100% specific for AOC from mTBI regardless if "head (was) struck" then the algorithm could simply be adjusted and data readily reanalyzed.

The VCU-rCDI-B may also be valuable to some clinicians, clinician extenders, and trainees who have minimal expertise in TBI evaluations and could be useful for administrative purposes such as estimating prevalence. Experienced clinicians are less likely to fully adopt a highly structured interview which may be perceived as less personal, more time consuming, and disruptive to the "art" of interview. Nevertheless, they may find certain elements of this instrument useful to incorporate into their own interview process. It is also important to note that study algorithm and its resulting operational definition of historical blast-related mTBI were based on the rating clinicians' interpretation of the interview responses. This consensus method

of "collective wisdom" served to negate the threat of inadequate inter-rater reliability but it did not negate the threat of collective bias. Furthering the concern for collective bias is that although they all trained at differing institution, the physician raters all practiced at the same institution at the time of the study. This and other internal validity threats could potentially be surmounted with a prospective study using immediate assessments to serve as the gold standard, but for which the combat theater setting presents an imposing logistical challenge.

Another limitation of this study was the small sample size, a total of 103 participants split into two samples. Confidence intervals are included to permit the readers to make their own conclusions about this limitation. Also the physician raters did not directly interview the participants and thus had to rely only on a completely open-ended interview in combination with the fully structured portion. The process did not permit the "art" of the interview with adjusting and shaping of questions based on the interviewee's responses and the interviewer's immediate interpretation. To permit this would have biased the interviewee by "priming" him/her for subsequent interviewers. The previously mentioned threat of recall bias could have been further confounded by symptom exaggeration from unknown secondary gain factors. While the algorithm minimized this to some extent by the aforementioned vetting of illogical responses, we did not specifically assess this with a validated symptom falsification measure. Lastly, in interpreting the inter-rater agreement data in this study the inherent limitations of the kappa and other agreement coefficients should be considered.[37] This includes biases due to the unbalanced proportion of the consensus mTBI positive versus consensus mTBI negative participants and varying patient and residual disease characteristics within our samples.

CONCLUSIONS

Expert physicians had widely varying degrees of agreement for their blinded ratings of the VCU-rCDI-B, a combined structured and unstructured interview for determining historical mTBI after blast exposure. To minimize the influence of inter-rater unreliablity and maximize transparency and standardization, we developed a diagnostic algorithm from the fully structured portion of the VCU-rCDI-B based on maximum fit with the consensus of the clinician ratings. By this algorithm, an individual was positive for probable prior blast-related mTBI if the endorsed memory gap pattern was consistent with the physiologic construct of PTA, or a witness observed LOC was endorsed, or when there were certain combinations of other AOC symptoms endorsed. Illogical memory gap patterns, illogical symptom durations, or having the stand-alone symptom "dazed" were deemed not indicative of AOC due to mTBI. The final algorithm had near perfect agreement vis-à-vis the proxy gold-standard clinician consensus ratings in a small cross-validation sample. The primary advantage of the VCU-rCDI-B as compared to unstructured or existing semi-structured interviews will likely be in research settings, especially multi-center studies. Additional testing of its psychometric properties of the algorithm component within independent groups of clinicians and comparison studies with other existing instruments is recommended.

Interview diagnosis of mTBI after blast

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Table 1: Sample Characteristics (maximum $N = 66$)

	Sample 1 (N=66)		Sample 2 (N=37)	
Characteristic	Count	Percent	Count	Percent
Sex				
Male	65	98	36	97
Female	1	2	1	3
Marital Status				
Married	31	47	17	46
Divorced	4	6	2	5
Single	31	47	18	49
Race				
Caucasian	56	85	29	78
African American	4	6	6	16
Other	6	9	2	5
Ethnicity				
Hispanic	10	15	4	11
Non-Hispanic	56	85	33	89
Level of Education				
"Non-High School"	1	2	1	3
High School Graduate	38	58	22	59
Some College	21	32	10	27
College Graduate	5	8	3	8
Post-Graduate Degree	1	2	1	3
Branch of Service				
Marine Corps (only)	49	74	30	81
Army (only)	12	18	6	16
Army and Marine Corps	1	2	0	0
Air Force (only)	1	2	1	3
Navy (only)	3	5	0	0
Number of Blasts				
1	19	29	4	11
2	12	18	11	30
3	13	20	4	11
4	4	6	3	8
5	1	2	1	3
More than 5	17	26	14	38

Table 2: Distributions of TBI Ratings – 4-Level Multinomial and Bivariate Outcomes

Sample 1 (n=66)						
Reviewers	mTBI with High Certainty	mTBI with Low Certainty	No mTBI with Low Certainty	No mTBI with High Certainty	mTBI	No mTBI
R1*	34 (52%)	15 (23%)	11 (17%)	6 (9%)	49 (74%)	17 (26%)
R2*	46 (70%)	12 (18%)	4 (6%)	4 (6%)	58 (88%)	8 (12%)
R3	24 (36%)	14 (21%)	12 (18%)	16 (24%)	38 (58%)	28 (42%)
R4	36 (55%)	20 (30%)	6 (9%)	4 (6%)	56 (85%)	10 (15%)
R5	51 (77%)	11 (17%)	2 (3%)	2 (3%)	62 (93%)	4 (6%)
Consensus					56 (85%)	10 (15%)

Sample 2 (n=37)						
Reviewers					mTBI	No mTBI
R1*	-	-	-	-	31 (84%)	6 (16%)
R2*	-	-	-	-	22 (59%)	15 (41%)
R4	-	-	-	-	29 (78%)	8 (22%)
R5	-	-	-	-	31 (84%)	6 (16%)
R6	-	-	-	-	32 (86%)	5 (14%)
Consensus					31 (84%)	6 (16%)

*Indicates study investigator

Table 3: Bivariate pairwise simple kappa's for each physician pair; probable mTBI or not TBI

			Sample 1			
Simple Kappa (ASE)	R1	R2	R3	R4	R5	R6
R1	1.00 -	0.47 (0.13)	0.50 (0.13)	0.51 (0.10)	0.31 (0.12)	-
R2	0.47 (0.13)	1.00 -	0.61 (0.14)	0.31 (0.0.9)	0.46 (0.18)	-
R3	0.50 (0.13)	0.61 (0.14)	1.00 -	0.39 (0.10)	0.37 (0.17)	-
R4	0.51 (0.10)	0.31 (0.09)	0.39 (0.10)	1.00 -	0.37 (0.17)	-
R5	0.31 (0.12)	0.46 (0.18)	0.37 (0.17)	0.37 (0.17)	1.00 -	-
			Sample 2			
R1	1.00 -	0.44 (0.13)	-	0.82 (0.12)	0.60 (0.18)	0.33 (0.15)
R2	0.44 (0.13)	1.00 -	-	0.19 (0.14)	0.37 (0.13)	0.47 (0.18)
R4	0.82 (0.12)	0.19 (0.14)	-	1.00 -	0.47 (0.18)	0.54 (0.18)
R5	0.60 (0.18)	0.37 (0.13)	-	0.47 (0.18)	1.00 -	0.68 (0.17)
R6	0.33 (0.15)	0.47 (0.18)	-	0.54 (0.18)	0.68 (0.17)	1.00 -

Abbreviations: ASE, asymptotic standard error; R1, reviewer 1; R2, reviewer 2; etc.

Table 4: Ordinal mTBI scale pairwise weighted kappa's for each physician pair.

	Sample 1 (Likelihood of mTBI; 0, 1, 2, or 3)				
Weighted Kappa (ASE)	R1	R2	R3	R4	R5
R1	1.00 -	0.54 (0.11)	0.62 (0.08)	0.64 (0.07)	0.44 (0.12)
R2	0.54 (0.11)	1.00 -	0.64 (0.09)	0.43 (0.07)	0.64 (0.12)
R3	0.62 (0.08)	0.64 (0.09)	1.00 -	0.49 (0.09)	0.54 (0.11)
R4	0.64 (0.07)	0.43 (0.07)	0.49 (0.09)	1.00 -	0.28 (0.08)
R5	0.44 (0.12)	0.64 (0.12)	0.54 (0.11)	0.28 (0.08)	1.00 -

Abbreviations: ASE, asymptotic standard error; R1, reviewer 1; R2, reviewer 2; etc.

Table 5: Distribution of rCDI-B Algorithm TBI Rating

Sample 1 (n=66)					
Rating	Count	Percent	Rating	Count	Percent
mTBI with PTA	43	65%	mTBI	55	83%
mTBI without PTA	12	18%			
No mTBI	11	17%	No mTBI	11	17%

Sample 2 (n=37)					
Rating	Count	Percent	Rating	Count	Percent
mTBI with PTA	19	51%	mTBI	30	81%
mTBI without PTA	11	30%			
No mTBI	7	19%	No mTBI	7	19%

Table 6: Cross-tabulation of rCDI-B Algorithm versus Physician Consensus Bivariate TBI Ratings

Sample 1 (n=66)			
	Physician Consensus		
Algorithm	mTBI	No mTBI	Total
mTBI	53 (80%)	2 (3%)	58 (83%)
No mTBI	3 (5%)	8 (12%)	8 (17%)
Total	56 (85%)	10 (15%)	66 (100%)

Sample 2 (n=37)			
	Physician Consensus		
Algorithm	mTBI	No mTBI	Total
mTBI	30 (81%)	0 (0%)	30 (81%)
No mTBI	1 (~~0~~3%)	6 (16~~9~~%)	7 (19%)
Total	31 (84%)	6 (16%)	37 (100%)

Figure 1. Diagnostic algorithm step 1, determination of traumatic brain injury with post-traumatic amnesia (PTA)

Figure 2. Diagnostic algorithm step 2, determination of traumatic brain injury without post-traumatic amnesia (PTA)

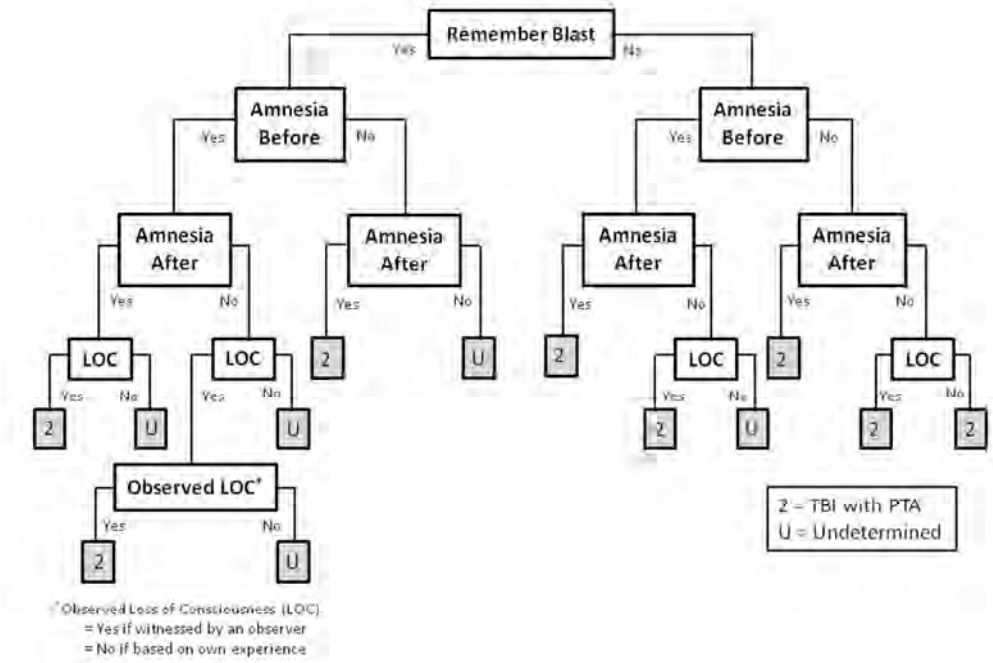

Figure 1. Diagnostic algorithm step 1, determination of traumatic brain injury with post-traumatic amnesia (PTA)
254x190mm (96 x 96 DPI)

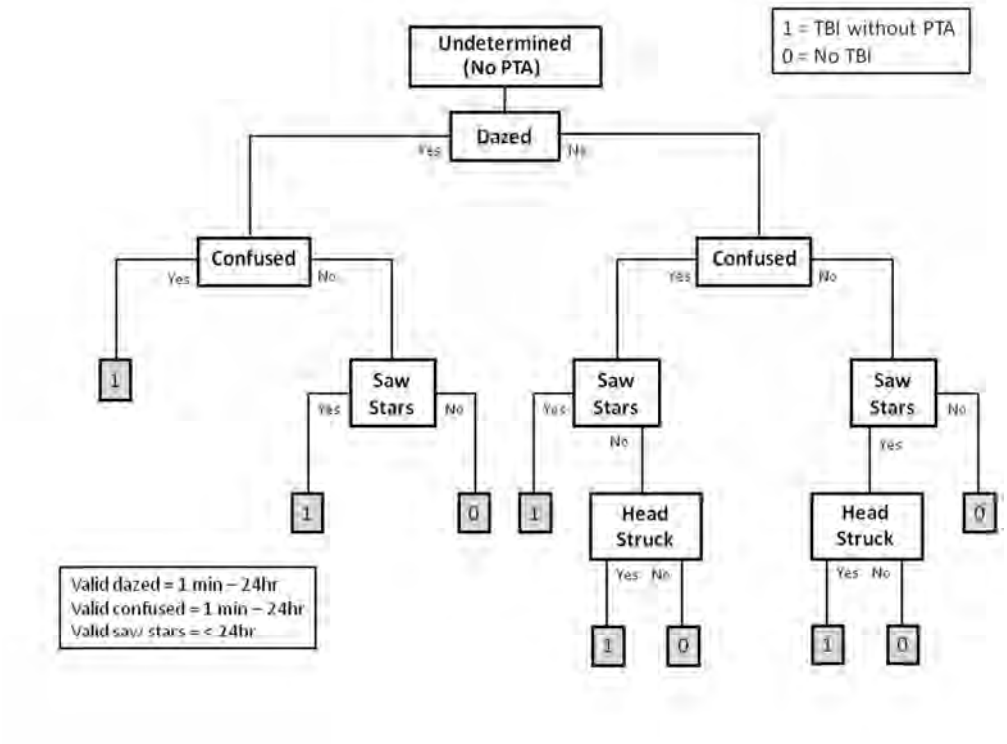

Figure 2. Diagnostic algorithm step 2, determination of traumatic brain injury without post-traumatic amnesia (PTA)
254x190mm (96 x 96 DPI)

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Retrospective Concussion Diagnostic Interview - Blast

Interviewer: _____

Introduction

I would like to spend the next 15 to 30 minutes asking some additional questions about this event *[blast event identified on screening]*.

Description of Event and Experience

1. You indicated on _____ *[date of blast experience]* that you experienced a blast during tour. You described it like this:

_____

_____

_____

_____

_____

[subject's description of the event for which he/she is presenting, or detected on screening]

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Description of Event and Experience (continued)

2. On the screening form, we asked you to describe this event and what you experienced in three sentences or less. Today, I would like you to tell me in as much detail as possible what happened to you and what you felt.
(Make sure to get a clear narrative about events leading up to the blast, information about the blast event, and information about what happened after the blast including what he/she experienced physically and emotionally).

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Recollection of Event

1. Do you have personal memory of the blast explosion itself?

O Yes
O No

If Yes, ask the following:

1a. Do you recall feeling a "blast wave" moving through your body?

O Yes
O No
O Don't Know

2. Is there a period of time just BEFORE the explosion for which you think you observed or experienced things but for which you have no memory at all?

O Yes
O No

If Yes, ask the following:

2a. What is the last thing that you personally remember occurring just BEFORE the blast?

2b. How long was the period of time between [the thing in 2a response] and the blast?

☐☐☐ O Seconds O Minutes O Hours

If subject responds in units other than those listed, record here: _____ *and convert later.*

If subject is unable to provide a measurable response to 2b then instruct him/her: I understand that this is time that you do not remember, but please give me your best guess. *Then repeat question 2b.*

If subject is STILL unable to provide a response then instruct him/her: Please try and make your guess by what other people may have later told you, or on events that you think passed during that time. *Then repeat question 2b.*

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Recollection of Event (continued)

3. Is there a period of time just AFTER the explosion for which you think you observed or experienced things but for which you have no memory at all?

○ Yes
○ No

If Yes, ask the following:

3a. What is the first thing that you personally remember occurring just AFTER the blast?

3b. How long was the period of time between the blast and [the thing in 3a response]?

☐☐☐ ○ Seconds ○ Minutes ○ Hours

If subject responds in units other than those listed, record here: _____ *and convert later.*

If subject is unable to provide a measurable response to 3b then instruct him/her: I understand that this is time that you do not remember, but please give me your best guess. *Then repeat question 3b.*

If subject is STILL unable to provide a response then instruct him/her: Please try and make your guess by what other people may have later told you, or on events that you think passed during that time. *Then repeat question 3b.*

4. *Interviewer: Review the prior answers. Are the responses **Yes** (#1), **No** (#2), and **No** (#3)?*

○ Yes
○ No

If Yes, ask the following:

4a. It sounds like there are no holes or gaps in your memory from that day, is that correct?

○ Yes
○ No

If No:

*Inform subject: "I need to understand how this fits with the earlier questions," then re-administer questions 1-3. If responses are still **Yes** (#1), **No** (#2), and **No** (#3), then contact a clinical research staff member to help intervene.*

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Retrospective Concussion Diagnostic Interview - Blast

Injury Mechanism

Advise the subject:
Some of the next questions may seem repetitive, but please bear with me, as we are trying to learn as much as possible about what you have experienced. If there are any questions where you are not sure of the answer, please try to give me your best guess.
(If subject states he/she has already told you the answer to any of the following questions, then read back the statement you think applies and ask if you got right, then insert/amend as he/she indicates.)

1. What were you doing at the time of the blast?

2. Were there others with you at the time of the blast? O Yes O No

3. Were you wearing a helmet at the time of the blast? O Yes O No

4. Were you wearing full body armor at the time of the blast? O Yes O No

5. Were you wearing ear protection at the time of the blast? O Yes O No

6. Were you positioned inside or on a vehicle at the time of the blast?
   O Yes
   O No
   If Yes, ask the following:
   6a. What kind of vehicle was involved?
   6b. Describe your position (in relation to the vehicle)?

7. Did you have any other cover at the time of the blast (other than or in addition to a vehicle)?
   O Yes
   O No
   O Don't Know
   If Yes, ask the following:
   7a. Describe the cover.
   7b. Describe your position (in relation to the cover)?

8. About how close were you to the blast? [ ][ ][ ] ft

   If subject responds in units other than feet record here:
   _____ *and convert to feet later.*

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Injury Mechanism (continued)

9. What direction from you was the blast?
- ○ Left
- ○ Right
- ○ Above
- ○ Front
- ○ Behind
- ○ Below
- ○ Don't Know

10. Were you thrown or knocked to the ground?
- ○ Yes
- ○ No
- ○ Don't Know

If Yes, ask the following:

10a. Estimate how far you were thrown: ☐☐☐ ft

If subject responds in units other than feet record here: _____ *and convert to feet later.*

11. Were you thrown against or knocked into something else?
- ○ Yes
- ○ No
- ○ Don't Know

If Yes, ask the following:

11a. Describe the vehicle, structure, etc:

12. To your knowledge, was your head struck or did your head hit something?
- ○ Head was struck
- ○ Head hit something
- ○ No
- ○ Don't Know

If head was struck or head hit something, ask the following:

Based on the answer to 10, ask either:
12a.[What struck your head?] *or*
[What did your head hit?]

12b. What side of your head was struck or hit?
- ○ Forehead
- ○ Back of the head
- ○ Face or chin
- ○ Left side
- ○ Right side
- ○ Don't Know
- ○ Other: _____

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Consciousness

1. Did you become unconscious, that is, you could not see, speak, and move for any period of time?
   - ○ Yes
   - ○ No

If Yes, ask the following:

2. Were you told this by a witness, or is your report of unconsciousness based upon your experience?
   - ○ Witness
   - ○ Own Experience

If Own Experience, ask the following:

2a. How did you determine you were unconscious?
- ○ Events that passed
- ○ Evidence from a watch, time on a phone, video, etc.
- ○ Guess
- ○ Other: _____

3. How long were you unconscious?

☐☐☐
- ○ Seconds
- ○ Minutes
- ○ Hours

If subject responds in units other than those listed, record here: _____ *and convert later.*

Symptoms

For this section, "experienced continuously" means that the symptom occurred to at least some extent every month since it began. If the symptom was totally gone for one month or more at some point after it started, then use the approximate date or time last experienced before it went away temporarily; do NOT code as continuous to current date.

1. Did you feel dazed?
   - ○ Yes
   - ○ No

If Yes, ask the following:

1a. How long after the blast did you start feeling dazed?

☐☐☐
- ○ Minutes
- ○ Hours
- ○ Days
- ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

1b. How long did it last?

☐☐☐
- ○ Minutes
- ○ Hours
- ○ Days
- ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

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Symptoms (continued)

2. Did you feel confused?

○ Yes ○ No

If Yes, ask the following:

2a. How long after the blast did you start feeling confused?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

2b. How long did it last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

3. Did you see stars?

○ Yes ○ No

If Yes, ask the following:

3a. How long after the blast did you start seeing stars?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

3b. How long did it last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

4. Did you feel dizzy?

○ Yes ○ No

If Yes, ask the following:

4a. How long after the blast did your dizziness start?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

4b. How long did it last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

5. Did you feel irritable?

O Yes
O No

If Yes, ask the following:

5a. Did you have any irritability **before** the blast?
O Yes
O No
If no, skip to Question 5c

5b. Did the irritability that you had before the blast get **worse** after the blast?
O Yes
O No
If no, skip to Question 6

If subject indicated increased irritability after the blast, include words in [brackets], otherwise leave out.

5c. How long after the blast did you start feeling [more] irritable?

[ ][ ][ ]
O Minutes
O Hours
O Days
O Months

If less than 30 seconds or immediate onset, code as 0 minutes.

5d. How long did the [increased] irritability last?

[ ][ ][ ]
O Minutes
O Hours
O Days
O Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

6. Did you lose your hearing in one or both ears?

O Yes
O No

If Yes, ask the following:

6a. How long after the blast did your hearing loss start?

[ ][ ][ ]
O Minutes
O Hours
O Days
O Months

If less than 30 seconds or immediate onset, code as 0 minutes. Likewise, if less than 30 seconds or immediate onset upon removal of hearing protection, code as 0 minutes.

6b. How long did it last?

[ ][ ][ ]
O Minutes
O Hours
O Days
O Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

7. Did you have ringing in one or both ears?

○ Yes
○ No

If Yes, ask the following:

7a. How long after the blast did the ringing start?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

7b. How long did it last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

8. Did you go blind?

○ Yes
○ No

If Yes, ask the following:

8a. How long after the blast did you go blind?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

8b. How long did it last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

9. Did your head ache?

○ Yes
○ No

If Yes, ask the following:

9a. Did you have any head ache **before** the blast?
○ Yes
○ No
If no, skip to Question 9c

9b. Did the head ache that you had before the blast get **worse** after the blast?
○ Yes
○ No
If no, skip to Question 10

If subject indicated increased head ache after the blast, include words in [brackets], otherwise leave out.

9c. How long after the blast did your [increased] headache start?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

9d. How long did the [increased] head ache last?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

9e. How long after the blast was the pain at its worst?

☐☐☐ ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

9f. Please rate the pain when it was at its worst on a scale of 0 to 10, where 0 is no pain and 10 is the worst possible pain.

0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○

NO PAIN — WORST POSSIBLE PAIN

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

10. Did you feel abdominal or stomach pain?
- ○ Yes
- ○ No

If Yes, ask the following:

10a. Did you have any abdominal or stomach pain **before** the blast?
- ○ Yes
- ○ No

If no, skip to Question 10c

10b. Did the abdominal or stomach pain that you had before the blast get **worse** after the blast?
- ○ Yes
- ○ No

If no, skip to Question 11

If subject indicated increased abdominal or stomach pain after the blast, include words in [brackets], otherwise leave out.

10c. How long after the blast did you feel [increased] pain?

[ ][ ][ ]
- ○ Minutes
- ○ Hours
- ○ Days
- ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

10d. How long did the [increased] pain last?

[ ][ ][ ]
- ○ Minutes
- ○ Hours
- ○ Days
- ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

10e. How long after the blast was the pain at its worst?

[ ][ ][ ]
- ○ Minutes
- ○ Hours
- ○ Days
- ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

10f. Please rate the pain when it was at its worst on a scale of 0 to 10, where 0 is no pain and 10 is the worst possible pain.

0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○

NO PAIN — WORST POSSIBLE PAIN

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

11. We have covered head, abdominal, and stomach pain. Did you feel any other physical pain?
- O Yes
- O No

If Yes, ask the following:

11a. What part or parts of your body were in pain?

If multiple parts were given in 11a, ask subject:

11b. What part was the most painful?

For the following questions, replace [body part] with the (most) painful part indicated in 11a/11b.

11c. Did you have any [body part] pain **before** the blast?
- O Yes
- O No

If no, skip to Question 11e

11d. Did the [body part] pain that you had before the blast get **worse** after the blast?
- O Yes
- O No

If no, skip to Question 12

If subject indicated increased pain after the blast, include words in [brackets], otherwise leave out.

11e. How long after the blast did the [increased] pain start?

☐☐☐
- O Minutes
- O Hours
- O Days
- O Months

If less than 30 seconds or immediate onset, code as 0 minutes.

11f. How long did the [increased] pain last?

☐☐☐
- O Minutes
- O Hours
- O Days
- O Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

11g. How long after the blast was the [increased] pain at its worst?

☐☐☐
- O Minutes
- O Hours
- O Days
- O Months

If less than 30 seconds or immediate onset, code as 0 minutes.

11h. Please rate the pain when it was at its worst on a scale of 0 to 10, where 0 is no pain and 10 is the worst possible pain.

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

NO PAIN — WORST POSSIBLE PAIN

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Retrospective Concussion Diagnostic Interview - Blast

Symptoms (continued)

12. Did you have any other feelings or problems that started or got worse right after the blast that I did not ask?

○ Yes
○ No

If Yes, ask the following:

12a. Other symptom:

12a1. How long after the blast did this symptom start?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

12a2. How long did it last?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

12b. Other symptom:

12b1. How long after the blast did this symptom start?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

12b2. How long did it last?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

12c. Other symptom:

12c1. How long after the blast did this symptom start?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds or immediate onset, code as 0 minutes.

12c2. How long did it last?

[ ][ ][ ] ○ Minutes ○ Hours ○ Days ○ Months

If less than 30 seconds, code as 0 minutes. If continuously experienced through today, note in margin, then code appropriately post-interview.

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Retrospective Concussion Diagnostic Interview - Blast

Outcome

1. To your knowledge, did you sustain any physical injury(s) from the blast?
   - O Yes
   - O No

If Yes, ask the following:

2. Did your injuries include a skull fracture or a brain bleed?
   - O Yes
   - O No
   - O Don't Know

3. What were your injuries?

4. What kind of treatment did you receive for your injuries? (specific medication, treatment of wounds, etc.)

5. Tell me all the places where you received treatment.

6. Were you placed into a medically induced coma as part of your treatment?
   - O Yes
   - O No
   - O Don't Know

If Yes, ask the following:

6a. What was the reason?

6b. How many days were you in a medically induced coma? ☐☐☐ days

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Retrospective Concussion Diagnostic Interview - Blast

Outcome (continued)

7. Were you evaluated by a medic after the blast event?
   - O Yes
   - O No
   - O Don't Know

8. Were you medically evacuated or treated after the blast at an aid station or other medical center "in country"?
   - O Yes
   - O No

9. Were you medically evacuated outside of the theater of operation for assessment or treatment due to injuries from the blast (e.g., evacuated to Landstuhl, Germany)?
   - O Yes
   - O No

10. Did you miss duty while you were being evaluated or treated?
    - O Yes
    - O No

If Yes, ask the following:

10a. How many days were you off duty? ☐☐☐ days

RUNNING HEAD: Pain and polytraumatic injury following combat

Correlates of Pain Symptoms Among Iraq and Afghanistan Military Personnel Following Combat-Related Blast Exposure

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Abstract

Pain complaints are highly prevalent among military service members and Veterans of the recent combat operations in Iraq and Afghanistan. The high comorbidity of pain and conditions such as posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) underscores the importance of a greater understanding of factors associated with complex polytraumatic injuries among military personnel. The present study aimed to identify correlates of current pain among 201 U.S. military personnel who reported at least one blast experience during combat deployment (M_{age} = 27.2 years, *SD* = 7.58). Theoretically derived subsets of variables were analyzed in successive hierarchical regression models to determine correlates of self-reported pain symptoms. Preliminary models evaluated demographic features, medical and injury characteristics (e.g., TBI classification), psychosocial history (e.g., trauma exposure), and psychiatric variables. A final model was then derived, in which older age, possible or probable mild TBI, depression symptoms, and PTSD re-experiencing symptoms emerged as significant correlates of pain. The findings further the understanding of polytrauma symptoms among military personnel by identifying specific patient characteristics and comorbidity patterns related to pain complaints. Increased awareness of demographic, psychiatric, or medical factors implicated in pain will enhance comprehensive clinical assessment and intervention efforts.

Key words: Blast Exposure, Combat, Depression, Military, OEF/OIF/OND, Pain, Polytrauma, Posttraumatic Stress Disorder, Trauma, Traumatic Brain Injury

Abbreviations: AOC - alterations of consciousness; BESQ - Blast Experience Screening Questionnaire; CES-D - Centers for Epidemiological Studies Depression Scale; ECMP - Events Checklist for Military Personnel; IED - improvised explosive device; LOS - loss of consciousness; OEF/OIF/OND - Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; PCL - posttraumatic stress disorder checklist; PPCS - persistent postconcussive syndrome; PTA - post-traumatic amnesia; PTSD - posttraumatic stress disorder; SF-MPQ - Short Form McGill Pain Questionnaire; SM - Service Members; TBI - traumatic brain injury; VA - Veterans Affairs; WRAMC BIQ - Walter Reed Army Medical Center Blast Injury Questionnaire

Correlates of Pain Symptoms Among Iraq and Afghanistan Military Personnel Following Combat-Related Blast Exposure

Introduction

A growing literature supports a relationship between pain conditions and psychiatric disorders such as depression and posttraumatic stress disorder (PTSD). Pain and PTSD are particularly significant problems for military Veterans; up to 20% of returning Veterans meet criteria for PTSD [1, 2], and moreover, data from a range of deployment eras suggest that up to 80% of Veterans seeking treatment for PTSD also experience pain [3-8]. Despite some differences in injury characteristics and pain locations that vary by deployment era, the results of previous work supports a relationship between the presence and severity of PTSD symptoms and increased pain level, pain disability, and poorer health outcomes among Veterans [3, 4]. However, among the active duty service members (SMs) and Veterans of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND), the association between pain and PTSD is further complicated by the sequelae of exposure to blasts, such as those caused by improvised explosive devices, rocket-propelled grenades, and other explosive munitions [9]. Blast-related injuries have emerged as one of the chief concerns for returning military personnel, resulting in a devastating, complex array of outcomes that includes neurocognitive difficulties associated with traumatic brain injury (TBI), psychiatric disorders, and pain syndromes, e.g., [6, 10]. Indeed, the complexity of these combat-related injuries has led some researchers to suggest that a polytraumatic injury profile (i.e., the presence of multiple injuries) may best describe the negative health consequences associated with recent combat operations, due to the fact that returning SMs and Veterans tend to experience multiple medical

problems [10]. Therefore, more study is needed to understand the unique risk factors and symptom comorbidity patterns in the context of polytraumatic injuries among OEF/OIF/OND military personnel in order to best inform prevention and secondary intervention efforts, particularly as these individuals increasingly begin to transition from active military service and seek ongoing health care.

Recent studies of pain, PTSD, and blast-related neurocognitive difficulties, including TBI and persistent postconcussive syndrome (PPCS), have found high co-occurrence of these conditions among OEF/OIF/OND Veterans. Results from two studies of nationally representative samples of OEF/OIF/OND Veterans enrolled in Veterans Affairs (VA) health care reveal high prevalence rates of psychiatric disorders (9.5-42%) and pain complaints (20-33%), with the prevalence of co-occurring PTSD and/or pain increasing significantly among Veterans with diagnosed TBI (54-73%) [10, 11]. Regarding specific polytrauma clinical samples, Lew and colleagues [6] determined that the co-prevalence rate of chronic pain, PTSD, and PPCS among OEF/OIF/OND Veterans was roughly 42%, indicating a high degree of comorbidity for these three conditions. In fact, the results suggested a higher likelihood of having concurrent diagnoses for two or all of the disorders than of receiving a diagnosis for any individual condition alone. Additional research conducted in other Veteran and civilian samples likewise suggests that pain and PTSD [12], and pain and depression [13] are more likely to manifest as comorbidities rather than as individual conditions.

Etiologic models of pain and comorbid disorders purport a complex interaction of biological and psychosocial factors, and considering the heterogeneity of polytrauma injuries, findings regarding symptom development and comorbidity models are mixed. Moreover, a variety of psychosocial factors have been linked to pain and related conditions. Prevalence of

pain symptoms and/or pain-related disability increases with age [14], and may also vary among other demographic characteristics, such as education [8, 15], socioeconomic status [16], and gender [8, 17]. Lifetime exposure to trauma and stress has been found to impact a variety of medical concerns, including lifetime prevalence of chronic pain, suggesting that exposure to stressful life events may be an important risk factor in the development of pain disorders [18, 19]. For example, individuals with co-occurring PTSD and pain report higher rates of physical or sexual abuse history and more chronic medical conditions compared with persons with neither disorder, and higher ratings of psychiatric distress when compared to those individuals with pain or PTSD alone [19]. Among OEF/OIF/OND Veterans, diagnoses of mood disorders, PTSD, substance use disorders, anxiety disorders, TBI, and a high body mass index were found to distinguish individuals with persistent (i.e., chronic) pain versus those with no pain [8]. However, other studies have not supported these risk and comorbidity models, suggesting that correlates of PTSD and pain symptoms are not fully understood. Despite finding substantial rates of positive PTSD, depression, and substance abuse screens in a sample of OEF/OIF/OND Veterans, Moeller-Bertram and colleagues [20] did not find any demographic, physical health, or mental health differences between individuals who screened positive for PTSD only and those who screened positive for both PTSD and pain.

Although empirical studies of pain and associated biological, social, and psychological risk factors have provided some clues to the development and correlates of pain disorders, more information regarding these relationships within the context of polytraumatic injury and military samples is needed. Identification of factors associated with current pain symptoms, such as lifetime exposure to stress or levels of current psychiatric distress, may yield important insights about potential vulnerability and maintenance factors that could complicate the course of

recovery following injury and the onset of pain conditions following combat. A better understanding of these factors in relation to the subjective experience of pain may be useful for both identifying those individuals at greatest risk for developing complex and persistent symptoms following combat, as well as developing complementary treatment approaches that address the significant overlap in common polytraumatic injuries.

To this end, the purpose of this study is to examine demographic, psychosocial, and life history predictors of pain in a sample of United States military service members who were exposed to a blast experience during their deployment, and who may or may not meet criteria for TBI or PPCS. Specifically, this study aims to determine correlates of current, self-reported pain symptoms by analyzing the relationships between pain and conceptually similar categories of potential comorbidity factors; the selection of variables was informed by previous work in this area, and includes analysis of demographic characteristics, blast exposure and injury history, lifetime traumatic event exposure, and psychiatric complaints. Although previous work has established the co-prevalence of pain and conditions such as PTSD and TBI, these studies have largely focused on prevalence rates of clinical diagnoses rather than patients' experience of symptoms or additional psychosocial factors that may play a role in pain outcomes.

The present study extends previous work regarding polytrauma injury prevalence rates and aims to add clarity to the understanding of pain in the context of polytraumatic injury by determining the factors related to SMs' and Veterans' subjective pain experience. Findings regarding the relative impact of various demographic, psychosocial, and medical/injury characteristics on pain symptoms among OEF/OIF/OND Veterans have been mixed, and this study is unique in that a broad range of variables is available for examination as potential correlates of current pain symptoms. Moreover, while the majority of previous studies have

relied on treatment-seeking VA samples, the present study sample consists of both active duty SMs and Veterans recruited from a variety of clinical and non-clinical locations, thereby potentially increasing generalizability of the findings. It is hypothesized that greater exposure to traumatic life events, more significant and complex medical history, including history of TBI, and psychiatric symptoms will be associated with increased self-reported pain complaints.

Methods

Data were collected as part of a Congressionally Directed Medical Research Program investigating blast exposure and injuries sustained during OEF/OIF/OND. Eligible military SMs and Veterans had a blast experience within the past two years while deployed in OEF/OIF/OND. The data analyzed in the current manuscript represent one aspect of a larger multi-part study that includes cognitive, balance, and electroencephalography testing of participants, as well as planned longitudinal follow-up of participants over the course of one year [21, 22].

Procedure

The participating agencies' Institutional Review Boards approved this study, and informed consent was obtained after the details of the study were thoroughly explained to participants. All participants completed a series of self-report questionnaires. Although some participants were enrolled at clinics, the research evaluations were separate from clinical care or compensation and pension processes. Research staff supervised completion of all the questionnaires and provided additional instructions as needed. Participants received nominal compensation for their time and effort.

Participants

SMs and Veterans were eligible if they had a blast experience within the past two years while deployed in OIF/OEF/OND. Participants were recruited via letters, advertisements, and

from ambulatory healthcare clinics at a mid-Atlantic VA Medical Center and at several Army and Marine Corps bases located in the mid-Atlantic region of the United States. Blast experience was defined as having any of the following symptoms or experiences occurring during or shortly after exposure to blast or explosion: dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, or medically evacuated. Individuals who reported symptoms suggestive of possible severe or moderate TBI were excluded from the present study (n = 4), and thus participants who may have sustained a TBI during their blast experience were considered to be in the mild TBI category. Severe or moderate TBI was defined as: more than 30 minutes of lost consciousness, brain bleeding or blood clot (i.e., abnormal brain CT scan), or amnesia for the first 24 or more hours after the event. At the closure of study enrollment, N = 238 participants passed the eligibility pre-screening and consented for study procedures. Of these, 22 participants either did not meet final eligibility or failed to complete the initial study evaluations, resulting in the final enrollment sample size of N = 216. At the time of the present analyses, data had been collected and authenticated for the first N = 201 participants who met study criteria.

Measures

Short Form McGill Pain Questionnaire (SF-MPQ) [23]. This pain rating scale consists of 15 pain descriptors (11 sensory, four affective) that are rated for intensity on a Likert scale from 0 (“none”) to 3 (“severe”). The scale yields three pain scores: a total pain score, which is a sum of all 15 items, and sensory and affective pain subscale scores. The total pain score is frequently used in research and clinical applications, with higher scores indicating greater severity of current pain symptoms. The SF-MPQ has been shown to have strong psychometric properties,

and it is sensitive to changes in pain scores over time and/or as a result of clinical intervention (Melzack, 1987). Internal consistency for the total SF-MPQ score in the current sample was good (Cronbach's $\alpha = 0.86$).

Prior Health and Demographics Questionnaire. A detailed health and demographics questionnaire was developed for the study. Questions assessed for basic demographic information (e.g., sex, age, marital status, race/ethnicity, education, military history) as well as selected psychiatric and medical history. Psychiatric questions asked whether the participant had ever been prescribed medications for a behavioral, emotional, or thought disorder, and whether s/he had ever received school help for conditions such as Attention Deficit/Hyperactivity Disorder or a learning disability. These questions were dichotomized (yes/no) for the statistical analysis. The medical questions included thorough assessment of concussions and/or head injuries that occurred either prior to the OEF/OIF/OND tour(s) or during deployment that were not related to a blast experience.

Blast Experience Screening Questionnaire (BESQ). Participants were queried on their traumatic blast experience(s) via the BESQ, which was developed for a larger epidemiologic study of blast exposures. The BESQ was adapted from the Walter Reed Army Medical Center Blast Injury Questionnaire (WRAMC BIQ) [24]. The WRAMC BIQ screens patients for previously unreported blast-related pathologic conditions via 19 questions regarding the blast itself, as well as pre- and post-blast symptoms including the presence of visual disturbances, headaches, dizziness, or hearing loss, distance from the blast, and degree of cover. The BESQ focuses on symptoms immediately after the blast exposure, and also inquires about alterations of consciousness (AOC) following the blast. The AOC questions were designed to assess three specific aspects of post-blast severity: memory gap, observer-reported loss of consciousness, and

continuous memory. Participants are asked to provide information on up to three separate blast events. In accordance with previous work with this scale [21], responses from the selected AOC questions indicating post-traumatic amnesia (PTA) or loss of consciousness (LOC) were combined to create a categorical index of three potential diagnostic groups of mild TBI: definite/probable TBI (two or three positive AOC items); possible TBI (one positive AOC item), and no evidence of TBI with either PTA or LOC (all three AOC items negative).

Trauma Exposure History. The Events Checklist for Military Personnel (ECMP) is a questionnaire developed specifically for this study that was used to identify distressing combat and non-combat events that met the DSM-IV Criterion A for PTSD (qualifying stressor). The ECMP differs from other traumatic events questionnaires [25, 26] in that items pertaining to combat events are listed separately from non-combat events. Although other trauma account measures have specific categories for warfare/combat, these measures offer limited detail about combat experiences, and there may be some confusion about incidents that may fit multiple categories (e.g., motor vehicle accident or injury during combat). Thus, the ECMP was developed for the present study as a tool to provide improved description of the specific combat-related trauma experiences reported by participants.

The 11-item combat experiences portion of the questionnaire queried for yes/no answers to nine specific combat experiences (e.g., "Witnessed the serious injury or death of enemy troops," "Experienced an improvised explosive device (IED) that was detonated"), one question that queried for "Other combat-related event," and a question that asked "Have you had any combat-related experiences like these that you feel you can't tell about?" A summary score of all "yes" answers yielded a total combat experiences score. Participants were also asked to respond yes or no to potentially traumatic events that occurred outside of combat. Thirteen specific

events (e.g., "Been a victim of a violent crime," "Experienced physical abuse from a family member, caretaker, or teacher") were queried, as well as questions for "Other" and "Have you had any other distressing or disturbing events that you feel you can't tell about?" Affirmative responses were summed to create a total non-combat traumatic experiences score. For both the combat and non-combat experiences, participants were asked to identify their most distressing combat and non-combat event, to report details related to that event, including emotional response to the event, and to rate their peritraumatic level of distress and their current level of distress on a Likert scale from 0 ("not at all") to 7 ("extremely").

Centers for Epidemiological Studies Depression Scale (CES-D) [27]. The CES-D is a brief self-report scale designed to assess depressive symptoms in the general population. The 20-item scale focuses on the affective component of depression, and is not designed to be sufficient for a clinical diagnosis of a major depressive episode; however, the CES-D is highly correlated with clinical ratings of depression and other related complaints. A cut-off score of 16 is indicative of significant depressive symptomatology. The scale has been well-validated in both clinical and general samples, and internal consistency in the current sample was excellent (Cronbach's $\alpha = 0.89$). The total score was used as a continuous variable in the analyses.

PTSD Checklist (PCL) [28]. The PCL is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Respondents are asked, "In the past month, how much have you been bothered by…" each symptom, rated on a Likert scale from 1 ("not at all") to 5 ("extremely"). In the current study, scores were calculated for each of the three PTSD symptom clusters (re-experiencing, avoidance/numbing, hyperarousal), and each criterion score was examined in relation to pain, given past studies showing differential relationships between pain and PTSD subscales [3, 29]. A total scale cut-off score of 50 is recommended in military samples as an

indicator of significant PTSD symptomatology. Internal consistency for each of the three PCL subscale scores in the current sample was good (Cronbach's αs = 0.83-0.86).

Statistical Analyses

The demographic data, SF-MPQ, selected blast experience and TBI data, trauma exposure history, PCL, and CES-D data were first analyzed with descriptive statistics in order to summarize the sample characteristics. A series of hierarchical regression analyses was then conducted to analyze defined clusters of variables as correlates of pain. Hierarchical models were conducted in order to best determine the relative contribution of each variable at each stage of the model. Four theoretically-derived predictor sets were chosen, and one regression was conducted for each predictor set: 1) demographics (i.e., age, race, marital status, education); 2) medical/blast/injury characteristics (i.e., history of psychiatric medication, history of ADHD or learning disorder, number of prior head injuries, number of deployment blast exposures, classification of combat-related TBI); 3) lifetime trauma exposure characteristics (i.e., total number of combat-related trauma exposures, peritraumatic and current ratings of distress related to worst combat trauma, total number of non-combat trauma exposure, peritraumatic and current ratings of distress related to worst non-combat trauma); and 4) psychiatric variables (i.e., depression, PTSD symptom clusters). Any significant variable from the preliminary regression models was then entered into a final regression model. The total score on the SF-MPQ was the dependent variable for each of the preliminary analyses and the final model.

Results

The sample consisted of 194 men and 7 women, who were on average 27.2 years of age (*SD* = 7.58). Many of the participants reported more than one deployment location. Descriptive

characteristics of the sample are presented in Table 1. The sample was exposed to a high number of both combat (M = 7.67, *SD* = 1.93) and non-combat (M = 3.52, *SD* = 2.01) potentially traumatic event types. The respondents reported high levels of PTSD and depression symptomatology, with the average total PCL and CES-D scores nearing or meeting criteria for clinically significant distress, M = 47.54 (*SD* = 14.67) and M = 17.95 (*SD* = 10.44), respectively. Using the diagnostic categorization of TBI based on AOC responses, *n* = 45 were considered to have possible TBI, and *n* = 66 were categorized as probable TBI, with the remaining *n* = 90 reporting no PTA or LOC following blast exposure. Participants reported an average SF-MPQ total score of 11.04 (*SD* = 7.82), indicating moderate levels of pain severity that are consistent with the scale's validation samples (Melzack, 1987). Head (*n* = 131), lower back (*n* = 91), and knee (*n* = 58) pain were the most commonly reported pain areas, followed by pain in the neck (*n* = 37), mid-back (*n* = 32), shoulder (*n* = 32), ankle (*n* = 19), and hip (*n* = 16) regions. Full results of each of the preliminary hierarchical linear regressions are presented in Table 2.

Demographics. Due to the small number of women in the sample, sex was not analyzed as a separate variable. From the demographic model, only older age was significantly related to pain severity, $F(8, 192) = 3.02$, $R^2 = 0.11$, $p < 0.01$, accounting for a relatively small amount of variance in the model. None of the other variables from this model were statistically significant.

Medical/Blast/Injury. As shown in Table 2, higher number of deployment blast exposures and more severe TBI classification were related to pain severity. In the overall regression model, $F(6, 194) = 5.01$, $R^2 = 0.13$, $p < 0.001$, a TBI classification of possible or probable TBI was associated with higher pain severity ratings.

Trauma Exposure. Results from Model 3 supported a relationship between higher ratings of current distress to the worst combat-related trauma and pain severity at the final step of the model, $F (6, 193) = 6.24$, $R^2 = 0.16$, $p < 0.001$.

Psychiatric. Higher CES-D total score and higher scores on the PCL re-experiencing symptom cluster were associated with pain severity in Model 4, $F(4, 196) = 18.64$, $R^2 = 0.28$ ($p < 0.001$). Compared to the results of the first three preliminary regression models, depression and PTSD re-experiencing symptoms appeared to account for a much larger proportion of variance in pain symptoms.

Final Model. Following the series of preliminary regression models, the significant predictors of age, number of deployment blast exposures, TBI classification, current rating of distress to the identified worst combat-related trauma, CES-D total score, and PCL re-experiencing subscale score were entered hierarchically into the final predictor set. In the final model (Table 3), the variables of older age, the classification of possible or probable mild TBI, higher CES-D total score, and higher PCL re-experiencing symptoms remained significant correlates of SF-MPQ total score in the final step of the model, $F(7, 193) = 14.80$, $R^2 = .35$, adjusted $R^2 = .33$, $p < 0.001$. The variables in the final model thus accounted for approximately one-third of the variance in current pain symptoms.

Discussion

The purpose of this study was to explore the correlates of self-reported pain severity in a sample of blast-exposed OEF/OIF/OND military SMs and Veterans. A number of complex psychiatric, cognitive, and physical symptoms may be associated with combat-related blasts, and the high occurrence of polytraumatic injuries among returning military personnel emphasizes the

need for a more complete understanding of variables that are associated with pain, particularly those that are potentially modifiable. Findings from the current study demonstrated a number of demographic, historical, and psychological factors that are related to current self-reported pain, namely: older age, possible or probable mild TBI with PTA or LOC, depression symptoms, and the re-experiencing symptoms of PTSD. This study builds on previous work by systematically analyzing theoretically similar subsets of potential pain correlates that encompassed a broad range of demographic, medical history, TBI characteristics, lifetime trauma exposure, and psychiatric symptoms. Our results are consistent with Higgins and colleagues' [8] study of persistent pain symptoms in OEF/OIF/OND Veterans, and suggest that similar risk factors play a role in current pain symptoms as in chronic pain complaints. Thus, the present study broadens the knowledge of patient factors and comorbid conditions associated with subjective pain complaints in both active duty military and Veteran samples; this knowledge is important for identifying individual difference factors that may be implicated in pain symptoms, and the results may be used to inform assessment and intervention efforts for pain conditions.

As expected, psychiatric symptoms associated with depression and PTSD emerged as significant correlates of pain. While the present findings are in line with prior research demonstrating an association between depression and pain, e.g., [13], the association between PTSD and pain is less clearly understood in the current literature. In this study, the re-experiencing symptoms of PTSD were the only symptom cluster that demonstrated a statistically significant association with pain. Past work on PTSD symptom clusters and pain has shown mixed results. For example, Burris and colleagues [30] found that the re-experiencing symptom cluster was not related to pain severity in an adult orofacial pain sample; rather, the avoidance/numbing cluster appeared to predict pain disability and severity through an

association with depression symptoms. However, other work has supported a relationship between re-experiencing symptoms and pain in Veteran samples [3, 29, 31]. Notably, in a sample of female Veterans, Asmundson and colleagues [29] found a particular association between re-experiencing symptoms and severe headache/migraine pain, and suggested that headaches may function as a somatic flashback, thereby impacting on the re-experiencing symptoms [29, 32]. Similarly, findings from investigations of pain and PTSD in Veterans theorize that pain symptoms may serve as actual or symbolic reminders of traumatic experiences, e.g., [3]. This association may be particularly salient when physical injuries are sustained alongside psychological injury, such as in the case of direct combat or a severe accident, and this finding may have important considerations for polytrauma rehabilitation. Therapies focused on restoring physical functioning and addressing areas of pain may inadvertently trigger distressing memories or emotions related to a traumatic event, and comprehensive rehabilitation approaches must consider the potential interdependence of these conditions. Future studies of interventions for PTSD and pain have the potential to reveal insights on the etiology of these co-occurring conditions by measuring the effects of treatment on one condition (i.e., PTSD) and assessing the potential symptom change of the other (i.e., pain).

Findings also supported the role of severity of exposure to physical or psychological potentially traumatic events, rather than breadth, in the association with pain symptoms. Total number of types of combat-related or non-combat potentially traumatic events was not significantly related to pain ratings; however, reported current emotional distress to the worst combat-related traumatic event emerged as a significant correlate of pain in a preliminary regression model. This association did not hold in the final regression model, which may be due to the high correlation between PTSD ratings and the current distress rating (Pearson *r*

coefficients = 0.48 - 0.58, $p < 0.001$), indicating that combat trauma-related distress was better accounted for by reported PTSD re-experiencing symptoms. Similarly, the total number of deployment blast exposures did not predict pain in the final model, but rather severity of effects potentially associated with these events, as determined by categorizations of possible or probable TBI. These findings are consistent, in part, with dose-response models of psychopathology following trauma exposure, in which the magnitude of an individual trauma or the cumulative effect of many traumas over the lifespan predict adjustment difficulties [33]. Although the relationship between past trauma exposure and pain has been supported in the literature, e.g., [18], less is known about the impact of repeated or severe trauma exposures on pain symptoms. This study offers important preliminary support for the relationship between severity of blast exposure characteristics and the degree of psychiatric distress related to trauma exposures on ratings of pain severity, rather than mere frequency of previous potentially traumatic event exposures.

It is noteworthy that although the focus of the current study was blast-related exposures, pain conditions among OEF/OIF/OND Veterans may not always result directly from a blast exposure, but rather from other types of combat-related injuries, such as gunshot wounds and injuries resulting from motor vehicle accidents, or from the cumulative effects of challenging field conditions (e.g., carrying heavy body armor and supplies) and multiple redeployments [34]. While TBI is perhaps one of the better known conditions reported among OEF/OIF/OND Veterans, with over 280,000 diagnosed cases since the year 2000 [35], recent reports by the Veterans Health Administration indicate that diseases of the musculoskeletal system are, in fact, among the most common diagnoses among those who have served in OEF/OIF/OND and who are seeking VA health care [36]. Musculoskeletal system complaints frequently include a variety

of pain complaints, and head, neck, back, shoulder, and knee pain have been found to be the most common pain complaints for those who served during OIF/OEF/OND [6]; findings from the current study are consistent with these reports. While the current study did not query the exact etiology or timing of the pain symptoms reported by the military personnel in our sample, the association between more severe TBI characteristics and pain complaints represents an area for more nuanced study; for example, more severe TBI characteristics may indicate greater blast exposure and injury, which directly results in increased pain due to the physical injury, or the relationship between TBI characteristics and pain may be mediated by a third variable, such as PTSD symptoms or musculoskeletal injuries. Longitudinal studies are needed to explore the interplay of these co-occurring symptoms across time in relation to discrete life events, such as blast and/or other potentially traumatic event exposures, and physical injuries. Notably, a number of reports suggest that chronic pain is greater in patients with mild TBI compared with those with moderate or severe TBI (see [37], for a review). However, this finding may be complicated by the fact that individuals with severe TBI may be less able to effectively communicate pain experience [38]. Our results suggest that more severe characteristics of mild TBI are associated with reported pain symptoms, but it is possible that this relationship may only be worsened up until a certain point.

These findings hold potentially important implications for clinical interventions for pain and co-occurring psychiatric and medical conditions in returning Veterans. To begin, consistent with previous work conducted among OEF/OIF/OND Veterans, these data demonstrate an extensive number of returning OEF/OIF/OND military personnel who endorse a high co-occurrence of medical conditions (i.e., possible or probable TBI), pain, and psychiatric symptoms (i.e., PTSD and depressive symptoms). These findings demonstrate a specific

association between PTSD re-experiencing symptoms and current self-reported pain. Thus, while previous work has highlighted the high concurrence of PTSD and pain [6, 11], results from the present study suggest that PTSD re-experiencing symptoms may have a unique relationship with pain; further study will clarify possible mechanisms (e.g., anxiety sensitivity, somatization) underlying this association that may represent potential interventional targets. Given the association between TBI characteristics, self-reported pain, and specific psychiatric symptoms (i.e., depression, PTSD re-experiencing symptoms), early clinical interventions may help prevent enduring psychiatric or medical conditions; this is an important area for further study.

Indeed, the high rate of polytraumatic injury among combat Veterans highlights the challenges for effective assessment and rehabilitation efforts. In particular, pain in the context of polytrauma can have widespread effects on disability and functioning, and there is limited evidence regarding the patient factors and comorbid conditions associated with pain-related outcomes [39]. The co-occurrence of pain and psychiatric disorders, for example, has been shown to have serious adverse implications for adaptive functioning, including greater intensity of pain and affective distress, higher levels of life interference, and greater disability than individuals with an independent disorder; this result has been demonstrated in both Veteran [40] and civilian samples [19, 41]. Pain symptoms may also hinder certain aspects of TBI rehabilitation; for instance, commonly used pain medications may cause cognitive side effects that interfere with the active rehabilitation process [39]. Preventative actions, such as screening pain patients for PTSD, depressive, or TBI symptoms, or asking mental health and TBI patients for pain ratings could potentially lead to earlier applications of multi-focused treatments that work to alleviate the interacting physical and psychological concerns. The focus on acute risk factors may help decrease the probability that acute symptoms will persist and become chronic

psychological or physical responses to trauma among post-deployment military personnel. Concurrent and/or complementary treatments may be preferred to sequential treatments for individual disorders; a more comprehensive approach to screening, assessment, and treatment may have greater success at alleviating the distress associated with one or more disorders, particularly if symptoms of one condition may exacerbate or maintain the other.

There were several limitations to this study that must be noted. Given the cross-sectional nature of the analyses, conclusions regarding causality and predictive ability of the demographic, historical, and psychosocial variables on pain symptoms are limited. Longitudinal study of symptoms and experiences over time will allow for a more complete understanding of pain risk factors and the development and maintenance of pain symptoms over time. Further, while self-report assessments can be helpful for assessing an individual's perceptions of distress and difficulties, a limitation of this assessment method is the potential bias in the respondents' self-report of their past experience and early symptoms. In particular, memory for blast exposure and pre- and post-blast experiences may be affected by the length of time between injury to our evaluation, thereby introducing recall bias. Another limitation is that the PCL and CES-D were developed as screening instruments for PTSD and depression, respectively, and consequently they have limited diagnostic specificity. However, these instruments can provide insights into a participant's subjective experience of psychiatric difficulties, and hold value in the assessment of mental health concerns. Future studies will benefit from gathering clinical interview data combined with self-report data in order to more fully assess symptoms from a formal diagnostic approach as well the participants' subjective distress. More comprehensive assessment of previous trauma and blast exposure may yield additional insights regarding the association between these past exposures and current subjective symptom reports. Finally, the study sample

of relatively young, primarily male, military SMs and Veterans reflects a particular composition of military personnel, and the findings may not generalize to the general population or even other military samples. While the current study had a relatively small sample size compared to other published epidemiological studies, the smaller sample allowed us to collect more comprehensive data on the participants and to explore a wide variety of variables associated with pain. The sample was specifically recruited based on exposure to a combat-related blast, and this may represent a particular selection bias that reflects a unique composition of military personnel with regard to field duties and/or personality variables that are most likely to become exposed to explosive munitions in the field. More work is needed to better understand the risk factors and correlates of pain in diverse samples.

Conclusion

The results from this study indicated a set of correlates of self-reported current pain ratings that include older age, possible or probable mild TBI with PTA or LOC, depression symptoms, and the re-experiencing symptoms of PTSD. These factors are indicative of the common polytrauma triad of TBI, psychiatric concerns, and pain found in OEF/OIF/OND Veteran samples, and results highlight the need for further work to understand the interplay of these conditions over time. The findings further the understanding of complex polytrauma injuries among military personnel by identifying specific patient characteristics and comorbidity patterns related to pain complaints. These results are important to pinpoint areas for future research and treatment development.

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JRRD at a Glance

A better understanding of individual difference factors and comorbid conditions related to pain may be useful for identifying individuals at greatest risk for developing complex and persistent symptoms following combat. The present study reveals that older age, mild traumatic brain injury characteristics, depression symptoms, and posttraumatic stress disorder re-experiencing symptoms are related to self-reported pain among military personnel exposed to blasts during combat. Clinical interventions frequently target pain, psychiatric, and traumatic brain injury symptoms separately; however, the significant associations between these conditions suggests that complementary treatment approaches that address the significant overlap in polytraumatic injuries may better meet Veterans' needs.

Table 1: Descriptive characteristics of the sample (N = 201)

	N	%
Gender		
Female	7	3.5
Male	194	96.5
Race		
White/Caucasian	160	79.6
Black/African American	29	14.4
Other	12	6.0
Marital Status		
Single	92	45.8
Married	91	45.3
Divorced	18	9.0
Education		
Non-high school	2	1.0
High school	105	52.2
Some college	69	34.3
College graduate	22	10.9
Post- graduate degree	3	1.5
Highest Rank		
E-1 to E-4	119	59.2
E-5 to E-7	67	33.3
E-8 to E-9	2	1.0
W-1 to W-5	2	1.0
O-1 to O-9	9	4.5
Other	2	1.0
Deployment Locations [a]		
Operation Enduring Freedom		
1 deployment	114	
2 deployments	30	
Operation Iraqi Freedom		
1 deployment	68	
2 deployments	27	
3 or more deployments	9	
Other Deployment Location	31	
Branch of Service [a]		
Army	83	
Navy	4	
Air Force	2	

Marines	114
SF-MPQ: M = 11.04, *SD* = 7.82	

Note: [a] Respondents reported more than one category. SF-MPQ = Short Form-McGill Pain Questionnaire

Table 2: Successive hierarchical linear regression models investigating demographic, medical and injury history, trauma exposure, and psychiatric variables as predictors of Short Form-McGill Pain Questionnaire ratings (N = 201).

	Model 1			Model 2			Model 3			Model 4		
Demographic Variables	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*B*	*t*
Age	.30±.07	.29**	4.27	.26±.08	.25**	3.41	.29±.08	.28**	3.68	.32±.09	.31**	3.60
Marital Status (0 = Single)												
Married				1.52±1.20	.10	1.27	1.28±1.20	.08	1.07	1.25±1.21	.08	1.04
Divorced				1.02±2.01	.04	.51	1.04±2.01	.04	.52	.94±2.03	.03	.46
Race (0 = White/Caucasian)												
Black/African-Am.							-2.85±1.54	-.13	-1.85	-2.78±1.54	-.13	-1.88
Other							-.89±2.25	-.03	-.39	-.92±2.27	-.03	-.45
Education (0 = High School)												
Some College										-.54±1.22	-.03	-.45
College										-1.55±1.95	-.07	-.80
R^2/Δ R^2		.08/.08			.09/.01			.11/.02			.11/.00	
Δ*F*		18.24**			.81			1.74			.33	

	Model 1			Model 2			Model 3			Model 4			Model 5		
Medical/Injury History	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*B*	*t*
Past Medication	2.37±1.2	.14	1.97*	2.37±1.21	.14*	1.96	2.46±1.21	.14*	2.03	1.85±1.22	.11	1.52	2.28±1.19	.13	1.92
ADHD/Learning				-.09±1.98	-.00	-.05	.10±1.98	.00	.05	.18±1.96	.01	.09	.54±1.89	.02	.29
Prior Number Head Injuries							-1.45±1.16	-.09	-1.25	-1.64±1.15	-.10	-1.43	-1.63±1.11	-.10	-1.47
Number Blast Exposures										.70±.27	.18*	2.54	.84±.27	.22*	3.15
TBI Classification (0 = no evidence)															
Possible TBI													3.87±1.36	.21*	2.84
Probable TBI													4.70±1.22	.28**	3.85
R^2/Δ R^2		.02/.02			.02/.00			.03/.01			.06/.03			.13/.08	
Δ*F*		3.87*			.00			1.56			6.43*			8.55**	

	Model 1			Model 2			Model 3			Model 4		
Trauma Exposure	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*
Total Combat Exposure	.23±.29	.06	.80	-.15±.28	-.04	-.54	-.17±.28	-.04	-.62	-.12±.28	-.03	-.42
Distress at Time of Worst Combat Trauma				.03±.31	.01	.10	.06±.31	.01	.18	-.07±.32	-.02	-.23
Current Distress to Worst Combat Trauma				1.44±.29	.37**	5.05	1.41±.29	.36**	4.89	1.39±.29	.35**	4.85
Total Non-Combat Traumas							.17±.19	.06	.90	.26±.20	.09	1.30

Distress at Time of Worst Non-Combat Trauma										.46±.32	.14	1.44
Current Distress to Worst Non-Combat Trauma										.13±.26	.05	.50
$R^2/\Delta R^2$		.00/.00			.13/.13			.13/.00			.16/.03	
ΔF		.64			14.37**			.81			3.25*	
	Model 1			**Model 2**			**Model 3**			**Model 4**		
Psychiatric Variables	*B± SE(B)*	*β*	*t*	*B± SE(B)*	*β*	*t*	*B± SE(B)*	*β*	*t*	*B± SE(B)*	*β*	*t*
CES-D Total	.35±.05	.47**	7.52	.24±.06	.32**	4.36	.19±.07	.26*	2.88	.20±.07	.27*	2.93
PCL Criterion B: Re-experiencing				.43±.12	.26**	3.58	.35±.14	.21*	2.56	.39±.15	.24*	2.57
PCL Criterion C: Avoidance							.15±.12	.13	1.27	.16±.12	.14	1.37
PCL Criterion D: Hyperarousal										-.09±.15	-.06	-.60
$R^2/\Delta R^2$		.22/.22			.27/.05			.27/.01			.28/.00	
ΔF		56.49**			12.79**			1.61			.35	

Note: ADHD=Attention Deficit-Hyperactivity Disorder; TBI=Traumatic Brain Injury; CES-D=Center for Epidemiologic Studies-Depression Scale; PCL=Posttraumatic Stress Disorder Checklist. *$p < .05$; **$p < .01$.

Table 3: Final hierarchical linear regression model with only significant predictors from previous analyses as predictors of Short Form-McGill Pain Questionnaire ratings (N = 201).

	Model 1			**Model 2**			**Model 3**			**Model 4**			**Model 5**			**Model 6**		
Demographic Variables	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*β*	*t*	*B*± *SE(B)*	*B*	*t*	*B*± *SE(B)*	*B*	*t*
Age	.30± .07	.29**	4.27	.27± .07	.26**	3.71	.29± .07	.28**	4.07	.25± .07	.24**	3.65	.18± .07	.18*	2.81	.18± .07	.18*	2.84
Number Blast Exposures				.50± .27	.13	1.88	.65± .26	.17*	2.49	.46± .26	.12	1.79	.45± .24	.12	1.85	.44± .24	.11	1.83
TBI Classification (0 = no evidence)																		
Possible TBI							3.49± 1.32	.19*	2.64	2.54± 1.31	.14	1.94	3.01± 1.23	.16	2.44	3.07± 1.21	.16*	2.53
Probable TBI							4.89± 1.18	.29**	4.15	3.54± 1.20	.21*	2.94	3.16± 1.13	.19*	2.79	3.34± 1.12	.20*	3.00
Current Distress to Worst Trauma										.96± .27	.25**	3.62	.44± .27	.11	1.65	.09± .29	.02	.31
CES-D Total													.26± .05	.35*	5.23	.20± .05	.27**	3.65
PCL Criterion B: Re-experiencing																.35± .13	.21*	2.68
$R^2/\Delta R^2$			.08/.08			.10/.02			.18/.08			.23/.05			.33/.10			.35/.02
ΔF			18.24**			3.54			9.31**			13.13**			27.33**			7.20*

Note: TBI=Traumatic Brain Injury; CES-D=Center for Epidemiologic Studies-Depression Scale; PCL=Posttraumatic Stress Disorder Checklist. *$p < 0.01$, **$p < 0.001$

Characterizing the effects of mTBI and PTSD on balance impairments in blast-exposed Service Members and Veterans using computerized posturography

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AT A GLANCE

One hundred and sixty six service members and Veterans with combat-exposure in the Gulf Wars were assessed for balance using computerized posturography. Balance was deficient in unique patterns for participants having mild traumatic brain injury (mTBI) or post-traumatic stress disorder (PTSD) when compared with those with neither diagnosis, and these deficits were amplified for participants diagnosed with both conditions. Computerized balance assessment offers an objective technique to examine the physiologic effects and provide differentiation between participants with combat-associated mTBI and PTSD.

Manuscript entitled: Characterizing the effects of mTBI and PTSD on balance impairments in blast-exposed Service Members and Veterans using computerized posturography

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ABSTRACT

The high rate of blast exposures experienced by US Service Members (SMs) during the Gulf Wars in Iraq and Afghanistan has resulted in frequent combat-related mild traumatic brain injury (mTBI). Dizziness and postural instability can persist after mTBI as a component of post-concussion syndrome (PCS), but also occur among the somatic complaints of posttraumatic stress disorder (PTSD). The goals of this study were to examine the use of computerized posturography (CPT) to objectively characterize chronic balance deficits after mTBI, and to explore the utility of CPT in distinguishing between combat and blast exposed participants with and without mTBI and PTSD. Data were analyzed from a subject pool of 166 combat exposed SMs and Veterans who had a blast experience within the past two years while deployed. Using nonparametric tests and measures of impairment, we found that balance was deficient in participants diagnosed with mTBI with posttraumatic amnesia (PTA) or PTSD versus those with neither, and that deficits were amplified for participants with both diagnoses. In addition, unique deficiencies were found using CPT for individuals having isolated mTBI with PTA and isolated PTSD. Computerized balance assessment offers an objective technique to examine the physiologic effects and provide differentiation between participants with combat-associated mTBI and PTSD.

INTRODUCTION

In Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND), US Service Members (SMs) have been subjected to a high rate of blast exposures, with explosive munitions accounting for 78% of wounded in action cases, the highest proportion for any large scale conflict (1). Traumatic brain injury (TBI) is one of the consequences of these blast exposures and is considered the "signature wound" of these Gulf War conflicts. Among deployed SMs and Veterans, 19% are estimated to have sustained a TBI (2). Mild TBI (mTBI), or concussion, is by far the most common category of TBI during these deployments, accounting for over 80% of cases (3), and up to 20,000 additional mTBIs occur in garrison annually (4). Although indexed as mild based on initial severity, nearly 20% of those sustaining mTBI will develop Post-Concussion Syndrome (PCS), a condition of persistent symptoms (≥ 3 months) that may include physical, cognitive and behavioral impairments (5, 6).

Among the many potential consequences of TBI, decreased balance is one of the more impactful on functional status, including capacity to return to work (7). Subjective dizziness and postural instability are common acutely and chronically after moderate-severe TBI (8), as well as mTBI, where it can persist chronically as a component of PCS (9). In moderate-severe TBI, objective impairment of early balance function is ubiquitous, can be measured on routine physical examination, and is predictive of rehabilitation outcome (10, 11). Objective balance impairments persisting months to years after moderate-severe TBI have also been documented on computerized posturography testing (CPT), a method of quantifying balance through body-weight shifts on a force plate under normal and altered sensory conditions (12). In sports-related

mTBI, objective balance deficits have been shown acutely (1-5 days) compared with both baseline and controls, using either the CPT sensory organization test (SOT) (13, 14) or the Balance Error Scoring System (BESS) (15). In these investigations, participants with mTBI have higher magnitudes of sway when deprived of accurate visual cues, and deficits may persist even after other neurologic symptoms have resolved (16). The multisensory nature of postural stability has led some investigators to conclude that abnormal postural stability suggests a multisensory or central cause of imbalance after mTBI (17). Importantly however, in all of these mTBI studies, the differences resolved within the first week. Additionally, there are no well-controlled sports or trauma studies showing objective balance deficits after mTBI beyond this acute timeframe (16).

Veterans and SMs with blast exposure and suspected mTBI also commonly report persistent dizziness, vertigo, clumsiness, and imbalance symptoms (9, 18, 19). However data on objective postural stability are sparse and generally lacking controls. Vanderploeg (20) demonstrated impaired tandem gait in Vietnam War Veterans with chronic dizziness after mTBI compared to controls. However, this study used archival data and self-identified mTBI, so the validity of the findings is unclear. In a case series of OEF/OIF/OND SMs with blast-associated mTBI, Hoffer (21) reported an 84% incidence of acute dizziness symptoms and a substantial portion had abnormal CPT-SOT scores more than 30 days after injury. Similarly, a range of studies without control comparisons have reported that between 46-74% of symptomatic Veterans with blast-associated mTBI of even longer duration (months to years post-injury) had abnormal SOT scores (22-24).

The frequency of co-morbidities associated with combat mTBI (25), which may also be linked to balance deficits, further complicates the identification of a consistent pattern of balance deficits

corresponding with blast-related mTBI. One of the most significant unstudied potential confounders is post-traumatic stress disorder (PTSD), which is found in up to one-third of OIF/OEF/OND combatants (26). Chronic dizziness is a common symptom among individuals with combat-associated PTSD (27). Although published CPT data are lacking for PTSD, it is well documented that postural instability is associated with anxiety disorders in general (28).

In summary, the objectivity of assessment provided by CPT may offer a means of both identifying and monitoring recovery of individuals with mTBI-associated balance deficits. But the few published studies that examine balance impairments in SMs and Veterans with mTBI have lacked appropriate controls with a history of combat deployment and blast exposure, and have not examined confounding factors such as PTSD. This raises questions about the confounding role of other combat and blast-related conditions in the findings to date, as well as the utility of objective CPT findings to either support the mTBI diagnosis, or monitor recovery from mTBI. In this investigation, we sought to characterize balance deficits after combat blast exposure (with and without TBI and/or PTSD) and to address the utility of using CPT to differentiate blast-exposed individuals with no diagnosed injury, mTBI, PTSD, or co-occurring mTBI and PTSD. It was hypothesized that there would be a unique pattern of balance deficits defined by CPT for individuals with chronic mTBI when compared to normal or individuals with PTSD.

METHODS

Participants: Participants were recruited via letters, advertisements, and from ambulatory health care clinics at the Hunter Holmes McGuire VA Medical Center (VAMC) in Richmond, VA, Fort Lee Army Base in Prince George County, VA, Quantico Marine Corps Base (MCB) in Prince William County, VA, and Camp Lejeune MCB in Jacksonville, NC. SMs and Veterans were eligible if they had a blast experience within the past two years while deployed in OIF/OEF/OND. Blast experience was defined as having any of the following symptoms or experiences during or shortly after exposure to blast or explosion: dazed, confused, saw stars, headache, dizziness, irritability, memory gap (not remembering injury or injury period), hearing loss, abdominal pain, shortness of breath, struck by debris, knocked over or down, knocked into or against something, helmet damaged, or medically evacuated. Severe and Moderate TBI were the only exclusion criteria and were defined as: More than 30 minutes in coma, brain bleeding or blood clot (abnormal brain CT scan), or none of first 24 or more hours after event remembered (Post Traumatic Amnesia [PTA] > 24 hours). Therefore participants either had blast exposure without sustaining TBI or had sustained at least one blast-related mTBI.

As part of a larger, prospective longitudinal investigation, all participants underwent a comprehensive baseline assessment to collect demographic information, medical history including injuries and care received during their military service, specifics of blast exposure, injury, care and sequelae, current symptoms and level of functioning, and physical examination including focused neurologic testing. For this study, data on injury diagnoses, presence of mTBI and PTSD, and balance testing were analyzed.

As part of a comprehensive baseline assessment, trained research assistants administered to most (n=107) participants standardized interviews to determine the diagnosis of current PTSD using

the Mini-International Neuropsychiatric Interview PTSD module (MINI; version 6.0) and the diagnosis of mTBI accompanying blast exposure using the VCU retrospective Concussion Diagnostic Interview-blast version (VCU rCDI-B). The MINI is a validated short structured diagnostic interview based on DSM-IV and ICD-10 criteria that was developed by psychiatrists and clinicians jointly in the United States and Europe (29). Each participant's PTSD diagnosis was determined using "relaxed" DSM-IV criteria that ignored the A2 criterion and simulates DSM-V(30). The VCU rCDI-B is a combined, unstructured and fully structured, interview designed to affirm the presence of a blast-associated mTBI, either with or without posttraumatic amnesia (PTA). For those with multiple blast-related experiences, the self-identified "worst" potential concussive event was selected for interview. The interview data were independently reviewed by five experienced TBI physicians who individually rated each blast exposure in reference to the DoD/VA common definition for mTBI (31). A consensus diagnosis was obtained for each participant based on the physician majority rating.

For this investigation, PTSD diagnosis and mTBI diagnosis data on the 62 non-interviewed participants were extrapolated from standardized questionnaires, the PTSD checklist (PCL), and the Blast Experience Screening Questionnaire (BESQ), respectively. The PCL is a validated and widely used measure of self-reported PTSD symptom severity (32, 33). The BESQ is a modified version of the Walter Reed Army Medical Center Blast Injury Questionnaire, which characterizes blast effects (34). For the PCL, >=58 was used to define PTSD because this cut-point gave the peak kappa value (k=0.54, 81% correct classification rate) in analysis of its receiver operating characteristics versus the MINI within the 107 interviewed participants (30). Similarly based on data from the interviewed participants, a combination of the alteration of consciousness items from the BESQ was used that gave the peak kappa (k = 0.59, 91% correctly

classified) versus the physician consensus. Further, based on our clinical experience and supporting data from the athletic mTBI literature (35), we assumed that those having mTBI with PTA would be most likely to experience long-term impairment commonly associated with blast injury. Using interview and BESQ data, we divided the participants with mTBI into those with PTA and those without PTA. The diagnosis of mTBI with PTA is referred to in the analyses as "blast mTBI" and the group with mTBI without PTA was combined with those diagnosed to have not sustained mTBI and referred to as "no blast mTBI."

Outcome Measures: All participants underwent complete balance testing regardless of underlying injury or diagnosis, history of dizziness or imbalance, or current difficulties. Postural stability and balance were measured with computerized posturography (CPT) on dual-plate force platform, the NeuroCom Smart Balance Master (NeuroCom; NeuroCom International, Inc, Clackamas, OR) The specific CPT test given was the Sensory Organization Test (SOT), which generates equilibrium scores that compare the largest anterior-posterior movements of the subject over the trial to a theoretical limit for six sensory condition tasks. The sensory conditions follow: 1. eyes open with a fixed surface and visual surroundings; 2. eyes closed with a fixed surface; 3. eyes open with a fixed surface and sway referenced visual surroundings; 4. eyes open with a sway referenced surface and fixed visual field; 5. eyes closed with a sway referenced surface; and 6. eyes open with a sway referenced surface and visual surroundings (Figure 1). Each subject performed three trials on the Balance Master for each of the 6 sensory conditions, resulting in 18 equilibrium scores, ranging from 0 (touching a support surface, shifting feet, or falling) to 100 (little or no sway). From these equilibrium scores, 7 outcome measures were derived; the average of the three trials for each of the 6 conditions (EQ1-EQ6) and an overall

composite score (COMP) calculated as a weighted average of the 18 individual equilibrium scores (conditions 1 and 2 are weighted 1/3 as much as conditions 3 through 6).

**** Insert Figure 1 About Here ****

Additionally, "impairment" was defined as scoring at or below the 20th percentile, as compared to the age-matched population of participants with no history of disequilibrium (data provided by the administration manual).

Statistical Analyses: All statistical analyses were conducted using SPSS Statistics version 21.0 (IBM SPSS). Data were assessed for normality using the Shapiro-Wilk test. As data were generally *not* normally distributed (or even transformed-normal), non-parametric Mann-Whitney U and Kruskal-Wallis tests were performed to determine if there were differences between groups in the outcome measures. When significant differences were found between groups, post hoc pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Mann-Whitney U Tests were also performed on split data, and chi-square tests were applied to examine associations between participant cohorts and impairment.

RESULTS

Demographic Data: Of the 169 combat-exposed research participants, two participants' data were removed due to missing outcome measures (both unable to tolerate test) and one subject's data were removed because the balance scores did not pass the validity test (equilibrium scores for tasks 5 or 6 were higher than for tasks 1, 2 or 3, pairwise) (36). Of the 166 remaining participants with complete data, 160 were male. The mean age of the participants was 27.5 years, with a standard deviation of 7.8 years. Twenty-seven participants were African-American, 127

were Caucasian, and the remaining 12 self-identified as "other." The median time since the self-identified "worst" potential concussive event was 11.6 months, with an interquartile range of 13.7.

Of the 166 participants, 33 had no blast mTBI, 47 had blast mTBI without PTA, and 86 had blast mTBI with PTA. Forty-six were diagnosed with PTSD. For the purposes of data analysis, four subgroups were created: no diagnosis of PTSD or blast mTBI with PTA (n=65); diagnosis of blast mTBI with PTA but not PTSD (n=55); diagnosis of PTSD but not blast mTBI with PTA (n=25), and diagnosis of both blast mTBI with PTA and PTSD (n=21; See Table 1).

**** Insert Table 1 About Here ****

Results: The SOT findings for all 166 participants with complete data were analyzed to characterize impairments on the 7 outcome measures and to contrast findings between the subject cohorts.

No blast mTBI vs. blast mTBI (with PTA): To explore whether individuals with blast mTBI exhibit balance deficits (regardless of the presence of PTSD), Mann-Whitney U tests were used to compare data for participants without blast mTBI (n=80) and those with blast mTBI (n=86) for each of the 7 outcome measures. Only EQ3 showed a significant between group difference (p=0.006; no blast mTBI median = 92.3, interquartile range = 4.67; blast mTBI median = 90.5, interquartile range = 8.0)

Next, a chi-square test for each of the seven measures was used to test for association between impairment and blast mTBI diagnosis. A statistically significant association (p-value < .05) was found between blast mTBI diagnosis and impairment for COMP, as well as for EQ3 and EQ5 (see Table 2).

**** Insert Table 2 About Here ****

PTSD vs. no PTSD: Similar analyses were performed for PTSD (regardless of the presence of blast mTBI). Mann-Whitney U tests were used to compare data for participants not diagnosed with PTSD (n=120) and participants diagnosed with PTSD (n=46) for each of the 7 outcome measures. The Mann-Whitney U tests showed significant differences for the COMP, EQ2, EQ4, EQ5, and EQ6 outcomes. In addition, chi-square analyses showed a significant association between impairment and PTSD according to the same five measures (Table 3).

**** Insert Table 3 About Here ****

Normals, isolated blast mTBI, isolated PTSD, and co-morbid blast mTBI/PTSD: As 21 participants had both blast mTBI and PTSD, the interaction between mTBI and PTSD was investigated. First, Kruskal-Wallis tests were performed to determine if there were differences in any of the equilibrium scores between the four mutually exclusive sets: participants diagnosed

with neither blast mTBI nor PTSD (Group 0; n=55); participants diagnosed only with blast mTBI (Group 1; n=65); participants diagnosed with only PTSD (Group 2; n=25); and participants diagnosed with both blast mTBI and PTSD (Group 3; n=21).

The Kruskal-Wallis tests showed significant differences between groups for COMP, EQ3, EQ4, and EQ6. (See Figures 2 and 3 for results for COMP and EQ3.) Post hoc analyses indicated significant differences between Groups 0 and 1 on EQ3, between Groups 0 and 2 on EQ4, and between Groups 0 and 3 on all four (COMP, EQ3, EQ4, and EQ6). There were no between group differences found for Groups 1, 2 and 3 in post hoc analyses.

To further investigate the interaction of blast mTBI and PTSD, individuals with co-morbid conditions (Group 3) were excluded and separate Mann-Whitney U tests comparing the data from participants having neither diagnosis (Group 0) with participants having either isolated blast mTBI (Group 1) or isolated PTSD (Group 2) were performed. The same tests were then performed excluding Group 0 and comparing Group 3 with either Group 1 or Group 2 to determine if co-occurring diagnoses would mask or amplify findings from the isolated injury groups.

Mann-Whitney U tests showed significant differences for COMP, EQ1, EQ2, EQ3, EQ4 and EQ6 when comparing Group 0 (having neither diagnosis) to Group 2 (isolated PTSD). In addition, using a chi-square measure of association, impairment had a significant association between Group 0 and Group 2 according to COMP, EQ2, EQ4, EQ5, and EQ6 (see Table 4).

**** Insert Table 4 About Here ****

In sharp contrast, Mann Whitney U tests showed no significant differential effect for PTSD when comparing data for participants diagnosed with isolated blast mTBI (Group 1) to those with co-morbid mTBI and PTSD (Group 3). Likewise, impairment was not significantly associated with PTSD when only considering those with blast mTBI according on any of the seven measures (see Table 4).

When the groupings were reversed and those having neither diagnosis (Group 0) were compared with isolated blast mTBI (Group 1), chi-square was significant for impairment according to COMP, EQ2, EQ3, EQ4, and EQ5 (see Table 5). Again in sharp contrast, impairment was not significantly associated with mTBI when only considering those with PTSD according to any of the seven measures.

**** Insert Table 5 About Here ****

Finally, to determine if participants exhibited differences between trials, Kruskal-Wallis Tests were performed for Groups 0 through 3 across the individual trials. No clinically significant results were found.

DISCUSSION

Traditionally, mTBI and PCS have been diagnosed by interview and physical examination proximate to the time of injury (e.g., in the emergency department); interview and physical examination days weeks or months post-injury; and/or neuroimaging. The ability to support the diagnosis of mTBI and assess the status of persistent difficulties from mTBI with

physiological measures would improve the objectivity and reliability of diagnosis, allow for monitoring of recovery, and facilitate the assessment of treatment efficacy. The utility of assessing and defining balance deficits acutely after mTBI with CPT is well documented. Given the frequency of balance-related complaints and clinical findings following mTBI, identifying patterns of postural instability using CPT may represent a means of accurately identifying and quantifying the severity of balance deficits that may need treatment. CPT has also been suggested as an objective assessment tool for identifying and tracking the late effects of mTBI. However, previously persisting balance deficits after combat-blast mTBI have only been demonstrated in uncontrolled research studies and case reports.

This is the first controlled study to examine the use of CPT to objectively characterize chronic balance deficits after mTBI and to explore the utility of CPT in distinguishing between combat and blast exposed Veterans and SMs with and without mTBI and PTSD. Key findings of this investigation include; 1) the characterization of balance deficits using CPT for participants having combat blast-associated mTBI with PTA or PTSD; 2) the confirmation of the amplification of CPT abnormalities in the face of both mTBI with PTA and PTSD; and 3) the identification of unique abnormalities on CPT for individuals with isolated mTBI with PTA or PTSD. These findings have potential implications for diagnostics, classifying residual mTBI related impairments, and establishing treatment needs for mTBI and PTSD related postural instability.

No blast mTBI with PTA vs. blast mTBI with PTA: Balance performance on CPT of participants having blast mTBI with PTA differed significantly from blast-exposed controls having no mTBI or having mTBI without PTA, even when confounded by PTSD. Uniformly,

when surveying a cohort of combat-exposed participants with and without PTSD, the median of Condition 3 (sway-referenced visual surround) Equilibrium scores of participants having mTBI with PTA were significantly lower than the group of controls having either no mTBI or having mTBI without PTA. Analyses of the incidence of balance impairment also revealed differences between these two groups for both the Composite score and Condition 5 Equilibrium scores.

Taken together, these results provide evidence that on average persons with a history of blast mTBI with PTA have reduced postural stability relative to those without it. They corroborate findings from sports concussion cohorts showing mTBI with PTA has a poorer prognosis than mTBI without PTA (35). As one would expect, given the high incidence of visual tracking deficits seen with mTBI (37), the CPT conditions targeting inaccurate visual feedback (Condition 3) or deprived visual and proprioceptive feedback (Condition 5) were particularly sensitive to mTBI with PTA. On the contrary, when normal visual inputs were available as in conditions 1 and 4, regardless of the presence of normal or altered proprioceptive input (a sense infrequently impacted by mTBI), there were no group differences. While PTSD did have effects on postural instability as seen on CPT, the effects from mTBI were still noted over the entire cohort suggesting these findings are specific to mTBI with PTA. These findings also support the work of Vanderploeg (20) that indicated long-lasting gait deficits after mTBI, and agree with the other recent reports regarding Veterans and SMs that posturography is among the most consistently affected measures of the vestibular and balance system after blast mTBI (22-24). Additionally, the fact that these participants were not specifically referred for balance impairments or dizziness provides an unbiased perspective on balance deficits after blast mTBI and strengthens the generalizability of the findings. These unique and consistent findings may be useful in supporting the diagnosis of mTBI, monitoring recovery of postural deficits after mTBI,

and assessing the impact of interventions for mTBI-related balance deficits.

PTSD vs. no PTSD: Balance performance on CPT of participants with blast-exposed PTSD differed significantly from blast-exposed controls without PTSD, even when confounded by mTBI. Uniformly, when surveying a cohort of combat-exposed participants with and without blast mTBI with PTA, the median Composite and Condition 2, 4, 5, and 6 (all of the eyes closed or moving platform conditions) Equilibrium scores of participants with PTSD were lower than those without PTSD. Taken together, these results provide evidence that persons with a history of PTSD have reduced postural stability relative to those without PTSD. As one would expect, given the diffuse impact of PTSD on attention, concentration, and the integration of sensory inputs on overall functioning, postural abnormalities on CPT were seen on almost all elements of testing. Impairments during both eyes open and closed suggest a multi-level deficit involving integration of vestibular, somatosensory, and visual information (i.e., the entire balance system). These findings echo those of the Jacob study of anxiety disorders and SOT (28), but in contrast to the specific deficits noted in that study for spatial anxiety in panic and agoraphobic disorders (condition 4 only), PTSD appears to have a global impact on postural stability that is not indicative of an overreliance on a particular information channel. This could reflect a general attentional bias toward the "imbalance" signal—a mismatch between the gravitational vertical and other sensory inputs and a form of danger signal. While mTBI did have effects on postural instability as seen on CPT, the effects from PTSD were noted over the entire cohort suggesting a distinctly different profile from mTBI. As above, the fact that these participants were not specifically referred for balance impairments or dizziness provides an unbiased perspective on balance deficits with PTSD and strengthens the generalizability of the findings.

Neither diagnosis, isolated blast mTBI with PTA, isolated PTSD, and co-morbid mTBI/PTSD: Postural instability impairments are seen in participants having isolated blast mTBI with PTA or PTSD, and are identifiable when compared to combat-exposed controls with neither diagnosis. While there appear to be unique patterns of CPT findings of abnormalities for both mTBI (Condition 3) and PTSD (Conditions 2, 4 and 6), there are also overlapping abnormalities (Condition 5 and the overall Composite scores). Unfortunately, for comorbid mTBI/PTSD, there appear to be only nominal abnormalities on the full range of scores compared to both isolated mTBI and PTSD that prevent the simple differentiation of the two conditions using CPT. In particular, when the investigation of balance deficits after blast mTBI with PTA were limited to the subpopulation of participants with PTSD, no differences could be seen, suggesting PTSD masks the mTBI effects. The same result was found in the subpopulation of patients having blast mTBI with PTA: no median differences in scores were found between participants that were diagnosed with PTSD and those that were not because mTBI masked the effects of PTSD. Thus, the CPT findings may be useful to explain some percentage of the variance contributing to the differential diagnosis of mTBI and PTSD but a more multimodal assessment tool may be needed to fully differentiate their effects.

Importantly, in individuals with both blast mTBI with PTA and PTSD, there is an overall amplification of abnormalities seen on CPT. Thus, individuals diagnosed with comorbid mTBI and PTSD would be expected to experience worse symptoms (dizziness), clinical findings (postural instability), and functional deficits (falls, inability to run) than those diagnosed with either of the conditions separately. Clinically, this may also be useful to identify individuals with significant persisting effects of PTSD and mTBI and may guide clinicians as to the specificity, intensity, and durations of services utilized to enhance recovery. While a standard course of

therapy to manage persistent postural instability due to distant blast mTBI with PTA may have a positive effect in individuals with isolated mTBI, it is likely that either a greater intensity or duration of these services may be needed in the face of concurrent PTSD, or a different type of services may be needed altogether. While the specifics of therapeutic adjustments have not been elucidated, the ability of CPT to objectively (and differentially) identify abnormalities will assist in both developing and assessing the efficacy of these needed treatments.

Effective coordination of movement and balance involves a complex interaction of the sensory, motor-programming, and musculoskeletal systems. Even minor impairments in integrating this information could ostensibly lead to significant disability (38). Persistent balance deficits, even if mild, can complicate recovery from brain injury by contributing to emotional distress. Even mild dizziness and balance problems are more highly associated with psychiatric comorbidity than other disturbances of sensory function, such as hearing loss (39). This relationship is believed to be due to the closely shared neural circuitry between spatial processing, balance control, and arousal (40), and may in part explain why severe TBI patients with balance problems have a poorer prognosis than those without (10). Many SMs and Veterans with mTBI balance deficits also have PTSD, and it is known that the combination of psychiatric and physical morbidities is particularly disabling (41). Thus, it is important to treat balance deficits when they occur, particularly if the individual is at risk for developing an emotional disorder. Therapies successful in alleviating balance problems may reduce long-term disability and also have downstream benefits for emotional outcomes.

This large, prospectively collected sample did not have selection bias based on complaints of imbalance or dizziness and represents the first sizable cohort of individuals with combat-associated, chronic mTBI with either a comparison sample of combat-exposed controls,

or assessment of the confounding effects of with PTSD. Despite the strengths of the study, there remain some limitations that prevent generalizability. These limitations include the following: 1) a single dataset from one medical center (albeit recruited from several military treatment centers and a Veterans Affairs Medical Center), 2) an almost exclusive male population, and 3) no "gold standard" for confirming the late diagnosis of chronic mTBI. These findings should be cross-validated in additional cohorts, including ones with significant female participants.

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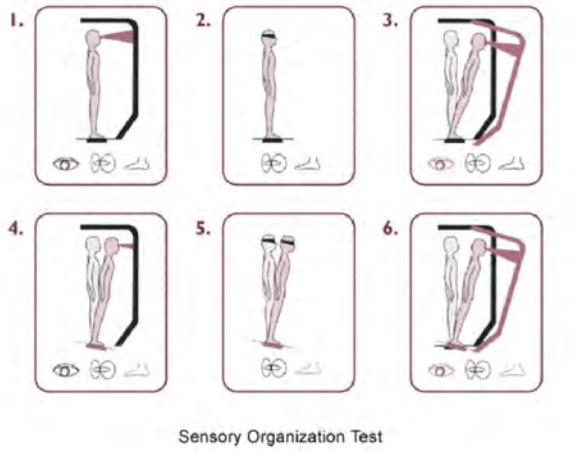
Figure 1

Sensory Organization Test - Six Conditions, courtesy NeuroCom® International, Inc.

1. Eyes open, fixed surface and visual surround.
2. Eyes closed, fixed surface.
3. Eyes open, fixed surface, sway referenced visual surround.
4. Eyes open, sway referenced surface, fixed visual surround.
5. Eyes closed, sway referenced surface.
6. Eyes open, sway referenced surface and visual surround



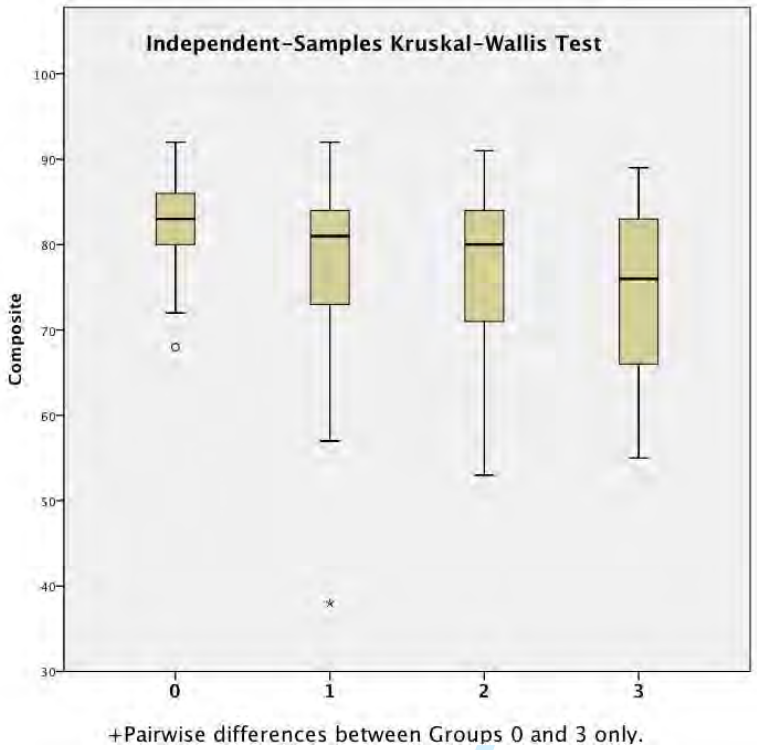


Figure 2: Boxplots of the composite score distributions for Groups 0 (neither diagnosis), 1 (isolated blast mTBI with PTA), 2 (isolated PTSD) 3 (comorbid mTBI and PTSD). Post-hoc tests show Groups 0 and 3 have significantly different medians.

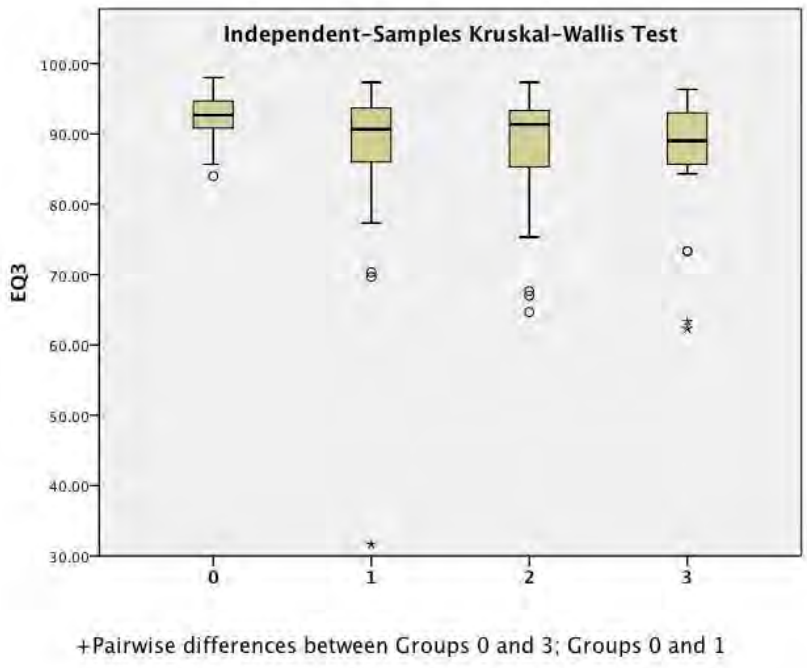


Figure 3: Boxplots of EQ3 for Groups 0, 1, 2 3 (x-axis). Post-hoc tests show Groups 0 and 1 have significantly different medians. Additionally, Groups 0 and 3 have significantly different medians.

Table 1: Descriptive Data by Diagnosis

Groups	Diagnosis	Male	Female	Mean Age (sd)	African American	White	Other ethnicity
0 n=55	No PTSD and no blast mTBI with PTA	50	5	26.3 (7.6)	9	43	3
1 n=65	Blast mTBI with PTA only	65	0	27.5 (6.6)	8	52	5
2 n=25	PTSD only	24	1	29 (10.7)	2	19	4
3 n=21	Blast mTBI with PTA and PTSD	21	0	29 (7.8)	8	13	0

Table 2: Association between blast mTBI with PTA and Impairment on SOT

Measure	Cut-point	No blast mTBI N (%) impaired	Yes blast mTBI N (%) impaired	Chi-square value	p-value*
COMP	75	18.75%	34.88%	5.46	0.019
EQ1	92	21.25%	24.42%	0.236	0.627
EQ2	88	23.75%	31.40%	1.209	0.271
EQ3	88	20.00%	33.72%	3.949	0.047
EQ4	76	22.50%	33.72%	2.571	0.109
EQ5	60	15.00%	27.91%	4.065	0.044
EQ6	57	12.50%	18.60%	1.169	0.28

Table 3: Association between PTSD and Impairment on SOT

Measure	Cut-point	No PTSD N(%) impaired	Yes PTSD N(%) impaired	Chi-square value	p-value*
COMP	75	22.50%	39.13%	4.654	0.031
EQ1	92	20.83%	28.26%	1.039	0.308
EQ2	88	23.33%	39.13%	4.143	0.042
EQ3	88	24.17%	34.78%	1.897	0.168
EQ4	76	23.33%	41.30%	5.291	0.021
EQ5	60	16.67%	34.78%	6.426	0.011
EQ6	57	11.67%	26.09%	5.235	0.022

Table 4: Association between PTSD and Balance (SOT) Impairment

	No blast mTBI n=80				**Yes blast mTBI n=86**			
Measure	**No PTSD N(%) impaired n=55**	**PTSD N(%) impaired n=25**	**Chi-square value**	**p-value***	**No PTSD N(%) impaired n=65**	**PTSD N(%) impaired n=21**	**Chi-square value**	**p-value***
COMP	10.91%	36.00%	7.103	0.008	32.31%	42.86%	0.778	0.378
EQ1	16.36%	32.00%	2.511	0.113	24.62%	23.81%	0.006	0.94
EQ2	14.55%	44.00%	8.234	0.004	30.77%	33.33%	0.048	0.826
EQ3	14.55%	32.00%	3.273	0.07	32.31%	38.10%	0.238	0.626
EQ4	14.55%	40.00%	6.386	0.011	30.77%	42.86%	1.038	0.308
EQ5	7.27%	32.00%	8.242	0.004	24.62%	38.10%	1.434	0.231
EQ6	7.27%	24.00%	4.397	0.036	15.38%	28.57%	1.823	0.177

Table 5: Association between blast mTBI with PTA and Balance (SOT) Impairment

	PTSD=0 n=120				PTSD=1 n=46			
Measure	**No blast mTBI N(%) impaired n=55**	**Yes, blast mTBI N(%) impaired n=65**	**Chi-square**	**p-value ***	**No blast mTBI N(%) impaired n=25**	**Yes, blast mTBI N(%) impaired n=21**	**Chi-square**	**p-value ***
COMP	10.91%	32.31%	7.823	0.005	36.00%	42.86%	0.225	0.635
EQ1	16.36%	24.62%	1.23	0.267	32.00%	23.81%	0.378	0.539
EQ2	14.55%	30.77%	4.383	0.036	44.00%	33.33%	0.545	0.46
EQ3	14.55%	32.31%	5.129	0.024	32.00%	38.10%	0.187	0.665
EQ4	14.55%	30.77%	4.383	0.036	40.00%	42.86%	0.038	0.845
EQ5	7.27%	24.62%	6.451	0.011	32.00%	38.10%	0.187	0.665
EQ6	7.27%	15.38%	1.902	0.168	24.00%	28.57%	0.124	0.725